(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 March 2006 (30.03.2006)

PCT

(10) International Publication Number
WO 2006/033633 A1

(51) International Patent Classification[7]: C07D 401/12, A61K 31/4184, A61P 25/22, 29/02, C07D 413/12, 413/14

(21) International Application Number:
PCT/SE2005/001405

(22) International Filing Date:
22 September 2005 (22.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/GB2004/004124
24 September 2004 (24.09.2004) GB
PCT/GB2004/004112
24 September 2004 (24.09.2004) GB
0500183-9 24 January 2005 (24.01.2005) SE

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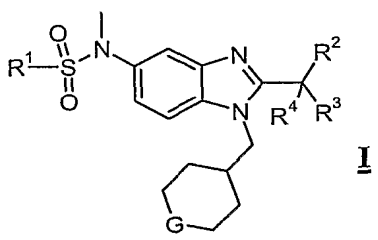
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOUNDS, COMPOSITIONS CONTAINING THEM, PREPARATIONS THEREOF AND USES THEREOF II



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(57) Abstract: Compounds of Formulae I, or pharmaceutically acceptable salts thereof: (I) wherein R^1, R^2, R^3, R^4 and G are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

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COMPOUNDS, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF II

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB_1 receptor, CB_2 receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominately in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB_1 receptor agonists, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB_1 receptors located in CNS. There are lines of evidence, however, suggesting that CB_1 agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB_1 receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB_1 receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "alkyl" refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-4}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, butyl, isobutyl, t-butyl.

The term "cycloalkyl" refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "alkoxy" refers to radicals of the general formula –O-R, wherein R is an alkyl. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and isobutoxy.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings sharing two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane,

homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

Preferably, the heterocycle is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 2 to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C_{2-6}heterocycle.

The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring,

more preferably, a monocyclic ring, wherein the ring comprises from 2 to 5 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C_{2-5}heterocycloalkyl.

The term "heterocyclyl" refers a monovalent radical derived from a heterocycle by removing one hydrogen therefrom.

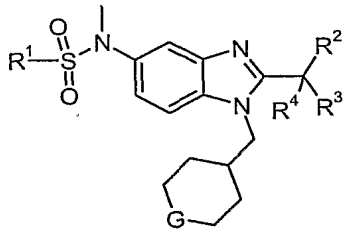
Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

"Acyl" refers to –C(=O)-R, wherein R is an alkyl. C_{2-5}Acyl groups include, for example, acetyl, propionyl, 2,2-dimethylpropionyl, and methyl-propionyl.

"Link," "linked," or "linking," unless otherwise specified, means covalently linked or bonded.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



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wherein

G is selected from –O-, -CHF-, and $–CF_2$-;

R^1 is a C_{2-6}heterocyclyl, wherein said C_{2-6}heterocyclyl includes at least one nitrogen on said C_{2-6}heterocyclyl ring, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{2-6}heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxy, R^5-C(=O)-, R^5-C(=O)-NH-, R^5R^6-NH-C(=O)-, R^5R^6-NH-C(=O)-NH-, R^5-O-C(=O)-, R^5-O-C(=O)-NH-, C_{1-6}alkoxy, and C_{1-6}alkylamino, wherein said R^5, R^6 are independently selected from –H, C_{1-6}alkyl, C_{6-10}aryl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, C_{2-6}heterocyclyl, halogenated C_{1-6}alkyl, and hydroxy-C_{1-6}alkyl; and

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

In another embodiment, the compounds are those of formula I, wherein

G is selected from –O- and $–CF_2$-;

R^1 is a C_{2-6}heterocycloalkyl, wherein said C_{2-6}heterocycloalkyl includes at least one nitrogen on said C_{2-6}heterocycloalkyl ring, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{2-6}heterocycloalkyl is optionally substituted with one or more groups selected from halogen, hydroxy, R^5-C(=O)-, R^5-C(=O)-NH-, R^5R^6-NH-C(=O)-, R^5R^6-NH-C(=O)-NH-, R^5-O-C(=O)-, R^5-O-C(=O)-NH-, C_{1-6}alkoxy, and C_{1-6}alkylamino, wherein said R^5, R^6 are independently selected from –H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, C_{2-5}heterocycloalkyl, halogenated C_{1-6}alkyl, and hydroxy-C_{1-6}alkyl; and

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

Another embodiment of the invention provides a compound of formula I, wherein

G is selected from –O- and $–CF_2$-;

R^1 is selected from C_{3-5}heterocycloalkyl and C_{2-5}heteroaryl, wherein said C_{3-5}heterocycloalkyl or C_{2-5}heteroaryl includes at least one nitrogen on said C_{3-5}heterocycloalkyl or C_{2-5}heteroaryl rings, respectively, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{3-5}heterocycloalkyl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from halogen, C_{1-3}alkoxy, C_{1-3}alkylamino and C_{2-5}acylamino;

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

A further embodiment of the invention provides a compound of formula I, wherein

G is selected from –O- and $–CF_2$-;

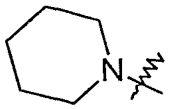
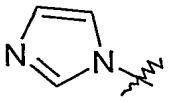
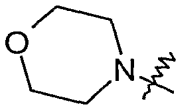
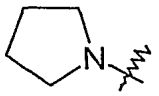
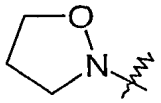
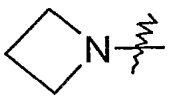
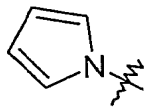
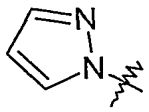
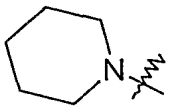
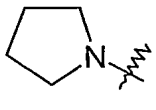
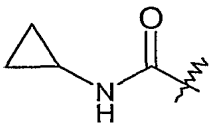
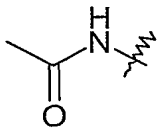
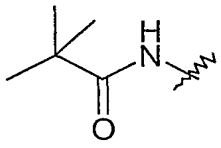
R^1 is selected from piperidinyl, imidazolyl, pyrazolyl, morpholinyl, pyrrolidinyl, azetidinyl, and isoxazolidinyl, wherein said piperidinyl, imidazolyl, pyrazolyl, morpholinyl, pyrrolidinyl, azetidinyl, and isoxazolidinyl are optionally substituted with one or more groups selected from fluoro and C_{2-5}acylamino;

R^2, R^3 and R^4 are selected from fluoro and methyl with a proviso that R^2, R^3 and R^4 are the same.

An even further embodiment of the invention provides a compound of formula I,

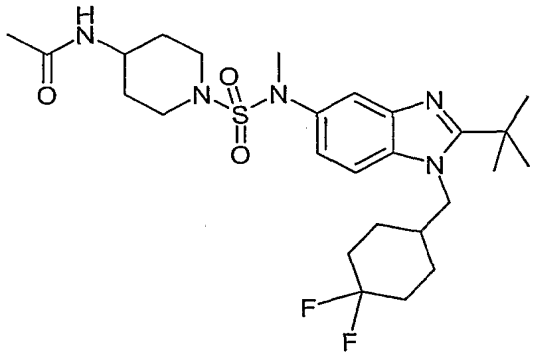
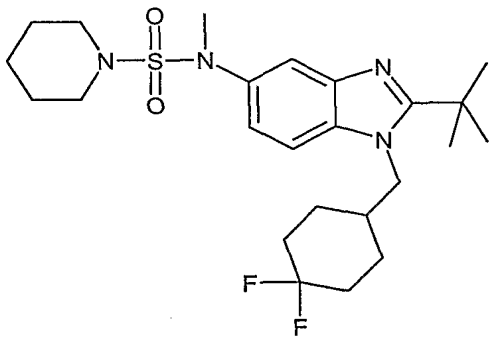
wherein

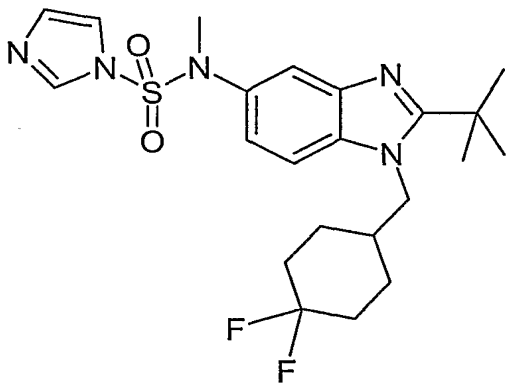
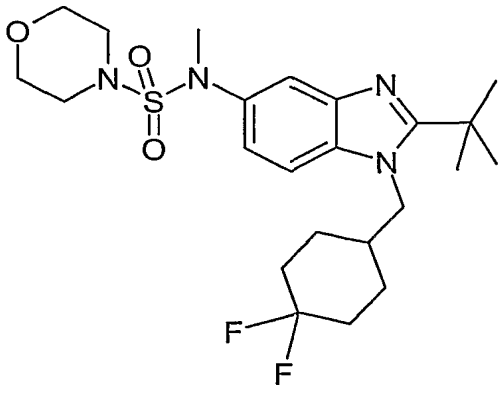
G is selected from –O- and $–CF_2$-;

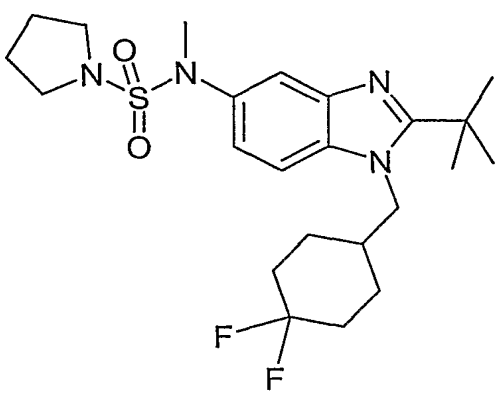
R^1 is selected from  ,  ,  ,  ,  ,  ,  and  ; wherein said  and  are optionally substituted by one or more groups selected from fluoro,  ,  and  ; and

R^2, R^3 and R^4 are selected from fluoro and methyl with a proviso that R^2, R^3 and R^4 are the same.

A further embodiment of the invention provides a compound selected from

 ,  ,

 ,  ,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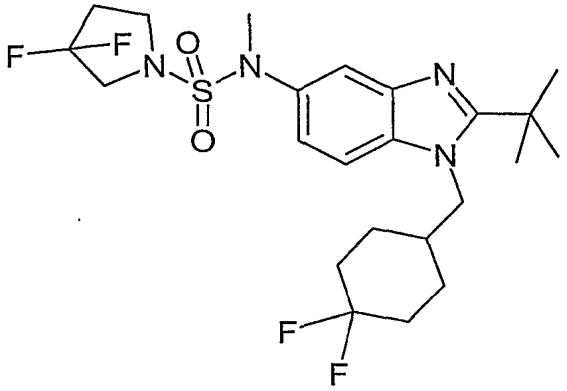
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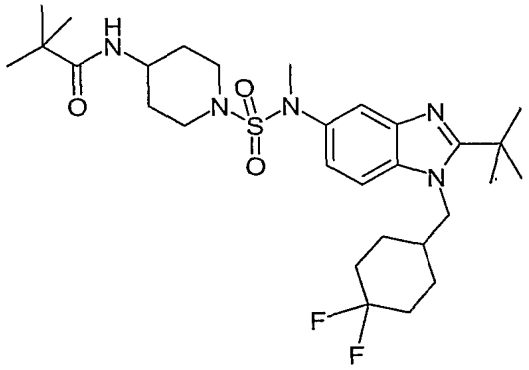
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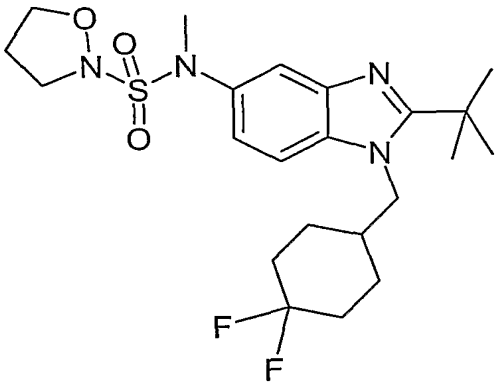
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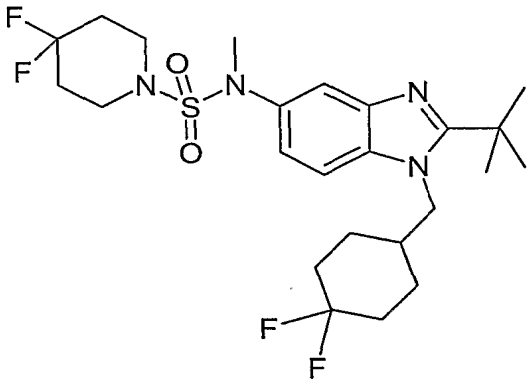
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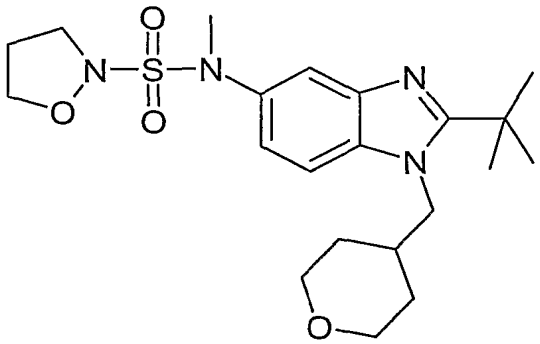
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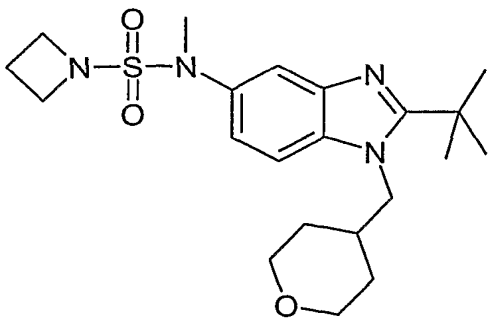
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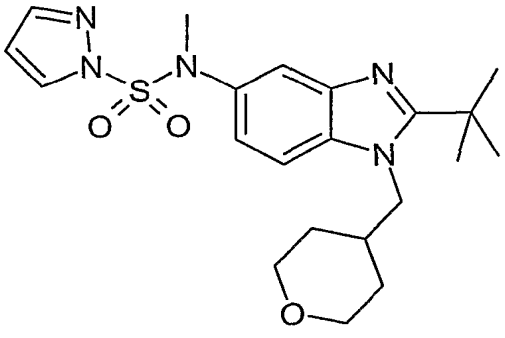

and

pharmaceutically acceptable salts thereof.

In another embodiment, the compound of formula I is selected from:

N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylmorpholine-4-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperidine-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide;

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylisoxazolidine-2-sulfonamide;

N-(1-{[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-pyrrolidin-1-ylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-1*H*-pyrrol-1-ylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperidine-4-carboxamide;

N-(*tert*-butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-diethylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperidine-4-carboxamide;
N-butyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2,2,2-trifluoroethyl)piperidine-4-carboxamide;
N-allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isobutylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxy-1-methylethyl)piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperidine-4-carboxamide;
Ethyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclopropanecarboxamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)-2-methylpropanamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclobutanecarboxamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)butanamide;

N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)propanamide;

Methyl 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidine-3-carboxylate;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]hexahydro-*N*-methyl-1*H*-azepine-1-sulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-*N*,4-dimethyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-(hydroxymethyl)-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-hydroxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-methoxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-hydroxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4,4-difluoro-N-methylpiperidine-1-sulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-3,3-difluoro-N-methylpyrrolidine-1-sulfonamide;

Methyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

(4R)-N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-hydroxy-N,4-dimethylisoxazolidine-2-sulfonamide;

N-(1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

N-(1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide;

tert-Butyl [1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]carbamate

tert-Butyl 4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxylate;

4-{[(Cyclopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide;

N-cyclopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide;

4-{[(isopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide;

N-isopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide;

N-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]acetamide;

2,2-Dimethyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide;

2-Methyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide;

4-Acetyl-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide;

4-(2,2-Dimethylpropanoyl)-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide;

N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylmorpholine-4-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpyrrolidine-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-3,3-difluoro-*N*-methylpyrrolidine-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylisoxazolidine-2-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4,4-difluoro-*N*-methylpiperidine-1-sulfonamide;

tert-Butyl 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperazine-1-carboxylate;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-4-{[(methylamino)carbonyl]amino}piperidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

4-Acetyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(2,2-dimethylpropanoyl)-*N*-methylpiperazine-1-sulfonamide;

4-Benzoyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(3-methylbutanoyl)piperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclopropylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-propionylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-isobutyryl-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclobutylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-butyryl-*N*-methylpiperazine-1-sulfonamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide;

N-(*tert*-Butyl)-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

N-butyl-4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

N-Allyl-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(cyclopropylmethyl)piperazine-1-carboxamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(1*H*-imidazol-1-ylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

Isopropyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)acetamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)-2,2-dimethylpropanamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)acetamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,4-triazole-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,3-triazole-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-4-carboxamide;

N-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methyl-1*H*-pyrazole-4-carboxamide;

N-(*tert*-Butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazol-3-yl)acetamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-imidazole-1-sulfonamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-imidazole-4-carboxamide;
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-3-carboxamide;
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropyl-1*H*-pyrazole-3-carboxamide;
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-3-carboxamide;
N-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-3-carboxamide;
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-3-carboxamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)piperazine-1-sulfonamide;
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperazine-1-carboxamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-pyrazol-1-ylcarbonyl)piperazine-1-sulfonamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylcarbonyl)piperazine-1-sulfonamide;
and pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will

further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonist of the CB_1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB_1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple

sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson's disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of

a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be contrued accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid and liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or table disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

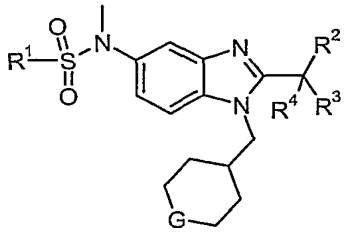
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

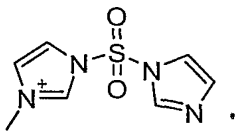
In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula I, comprising:

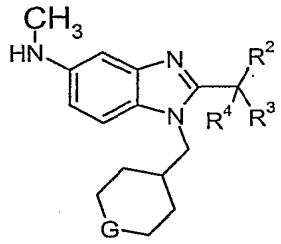


I

reacting a compound of Formula II with a compound of formula III,



II

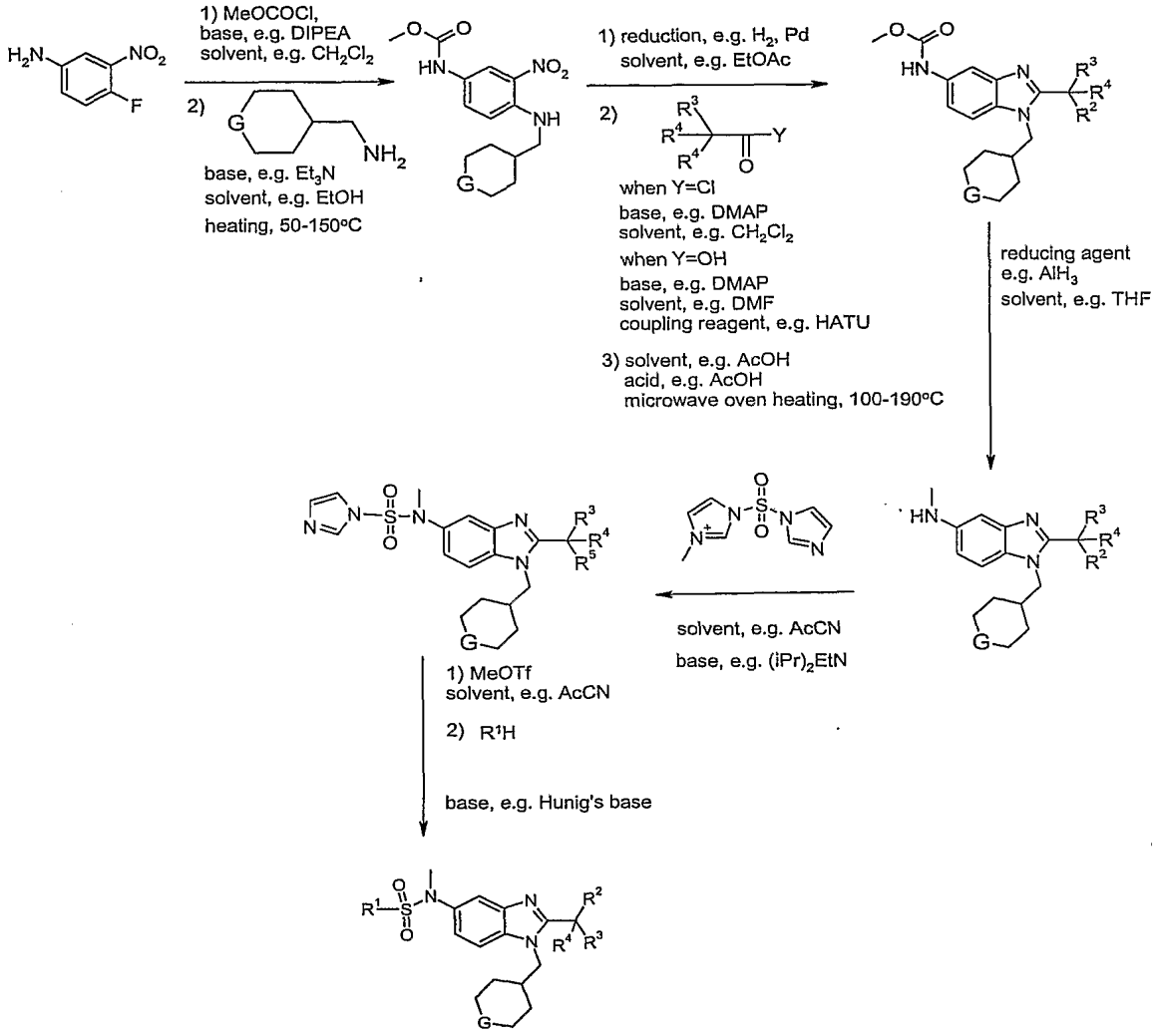


III

followed by treating the reaction product with MeOTf and subsequently with R^1H, wherein R^1, R^2, R^3, R^4 and G are as defined above.

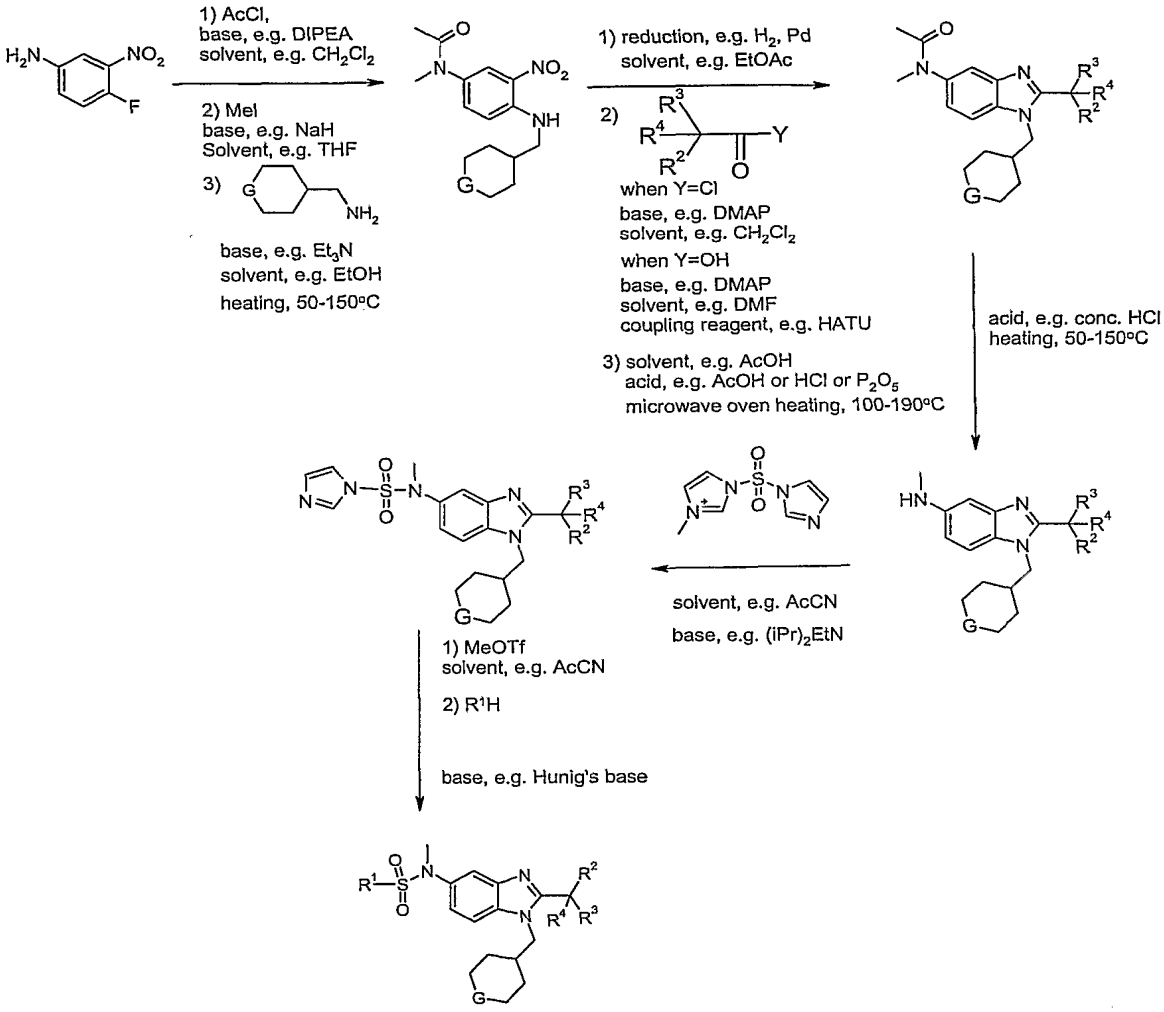
Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1-5.

Scheme 1



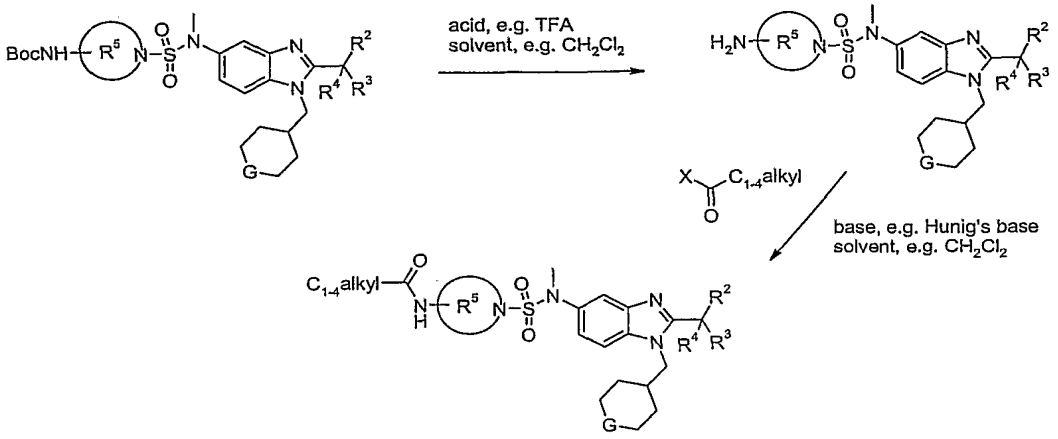
G, R^1, R^2, R^3 and R^4 are as defined above.

Scheme 2

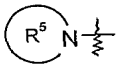


G, R^1, R^2, R^3 and R^4 are as defined above.

Scheme 3



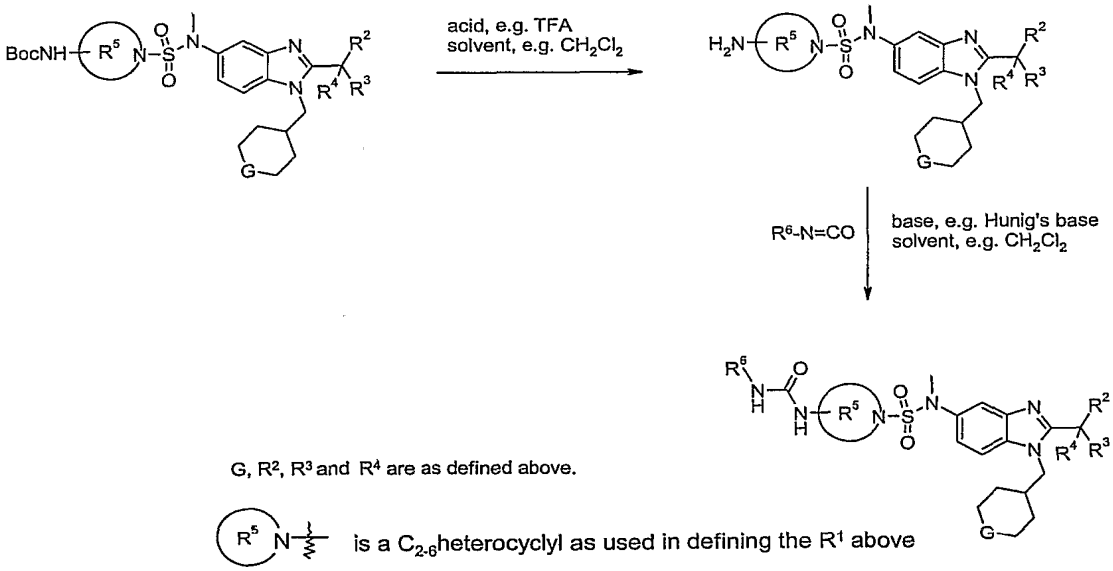
G, R^2, R^3 and R^4 are as defined above.



is a C_{2-6}heterocyclyl as used in defining the R^1 above

X is Acyl-O- or halogen

Scheme 4

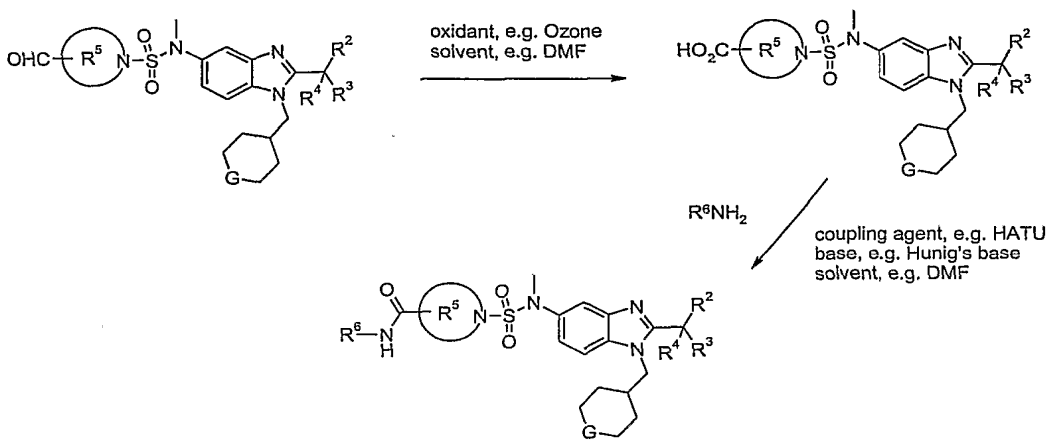


G, R^2, R^3 and R^4 are as defined above.

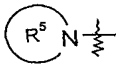
is a C_{2-6}heterocyclyl as used in defining the R^1 above

X is Acyl-O- or halogen

Scheme 5



G, R^2, R^3 and R^4 are as defined above.
R^6 is C_{1-6} alkyl or C_{3-6} cycloalkyl

 is a C_{2-6}heterocyclyl as used in defining the R^1 above

X is Acyl-O- or halogen

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor from BioSignal (hCB_2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

hCB_1 and hCB_2 GTPγS binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The EC_{50} and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of $GTPg^{35}S$ per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB_2) or 10 µM (hCB_1) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB2) or 112.5 µM (hCB_1) GDP prior to distribution in plates (15 µM (hCB_2) or 30 µM (hCB_1) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$Ki = IC_{50}/(1+[rad]/Kd)$,

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

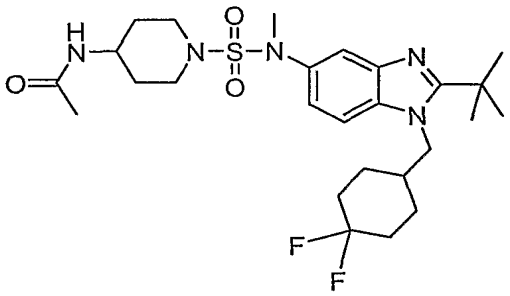
Using the above-mentioned assays, the Ki towards human CB_1 receptors for certain compounds of the invention are in the range of between 1 nM and 2897 nM. EC_{50} for these compounds are in the range of between 0.58 nM and 7647 nM. Emax for these compounds are in the range of between 72% and 161%.

EXAMPLES

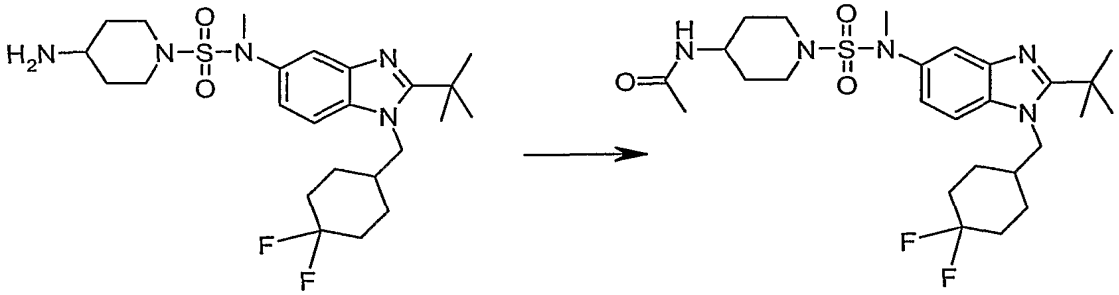
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

***N*-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide**



Step A: *N*-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide



Acetic anhydride (2.0 mmol) was added into a solution of triethylamine (2.0 mmol) and 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide (crude product from step J, 0.9 mmol) in CH_2Cl_2 (20 mL). After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then purified by silica gel chromatography (AcOEt to MeOH/AcOEt (1:9)) to give *N*-(1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide as a solid (235 mg, 48 % for

steps A-D). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.28 (m, 2H), 1.40-1.76 (m, 8H), 1.64 (s, 9H), 1.88 (s, 3H), 2.04 (m, 2H), 2.24 (m, 1H), 2.90 (m, 2H), 3.28 (s, 3H), 3.68 (m, 3H), 4.50 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H).

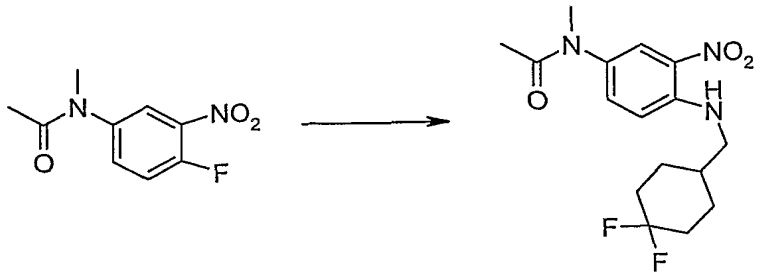
Step B. ***N*-(4-Fluoro-3-nitrophenyl)acetamide**

4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added in portions to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, J=6.44, 2.73 Hz, 1 H).

Step C. ***N*-(4-Fluoro-3-nitrophenyl)-*N*-methylacetamide**

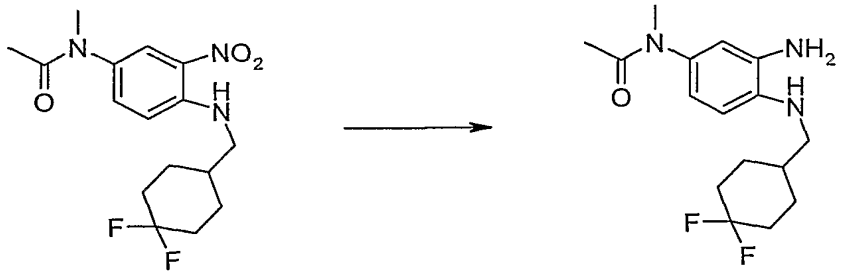
Sodium hydride (2.40 g, 60 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide (7.93 g, 40 mmol) in THF (120 mL) at 0 °C. Stirring for 20 min, iodomethane (17.0 g, 120 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturaed $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, 8.73 g (100%) of the title compound was obtained as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

Step D. ***N*-(4-{[(4,4-Difluorocyclohexyl)methyl]amino}-3-nitrophenyl)-*N*-methylacetamide**



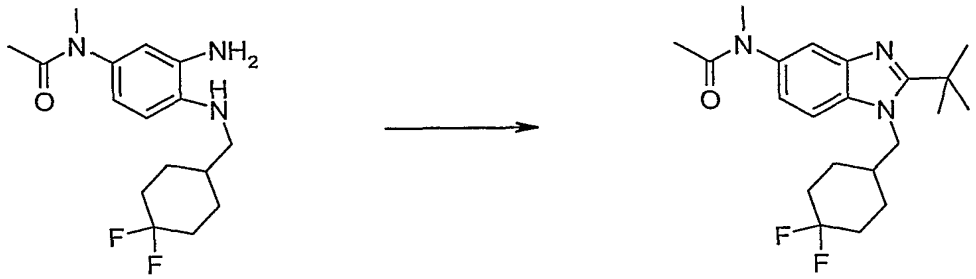
[(4,4-difluorocyclohexyl)methyl]amine TFA salt (780 mg, 2.96 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (628 mg, 2.96 mmol) and DIPEA (1.29 mL, 7.40 mmol) in EtOH (15 mL) at room temperature. The reaction mixture was heated for 18 hrs at 70 °C. Removal of the solvent, the crude product was purified by MPLC using EtOAc/Heptane 70-100% to give 855 mg (85%) of the title compound as an orange-red solid (84%). MS (ESI) $(M+H)^+$: 341.96.

Step E. *N*-(3-Amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)-*N*-methylacetamide



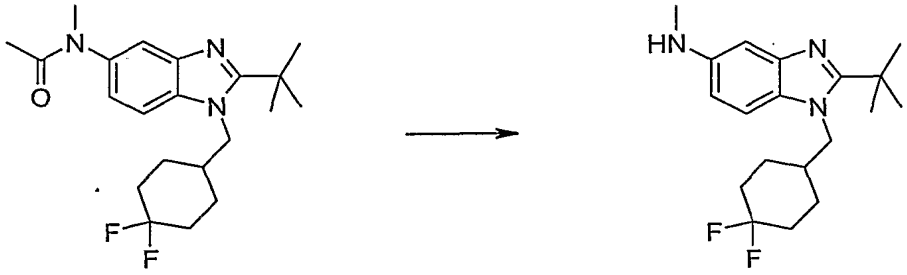
N-(4-{[(4,4-Difluorocyclohexyl)methyl]amino}-3-nitrophenyl)-*N*-methylacetamide (855 mg, 2.50 mmol) was hydrogenated in ethyl acetate (50 mL) catalyzed by 10% Pd/C at 50 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 716 mg (92%) of a white solid was obtained, which was used in the next step without further purification. MS (ESI) $(M+H)^+$: 311.99

Step F. *N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylacetamide



Trimethylacetyl chloride (0.29 mL, 2.41 mmol) was dropwise added to a solution of *N*-(3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)-*N*-methylacetamide (716 mg, 2.30 mmol) and Et_3N (0.38 mL, 2.75 mmol) in dichloromethane (100 mL) at 0 °C. The resulting mixture was stirred for 4h at room temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (16 mL) and then divided to 4 sealed test tubes. The mixture was heated at 150°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3 hrs. The combined reaction mixture was evaporated and then dissolved in EtOAc (200 mL), washed with saturated sodium bicarbonate solution, brine and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by MPLC using MeOH 5% and acetone 10% in DCM as eluent on silica gel to give 570 mg (65%) of the title compound as a white solid. MS (ESI) $(M+H)^+$: 378.23.

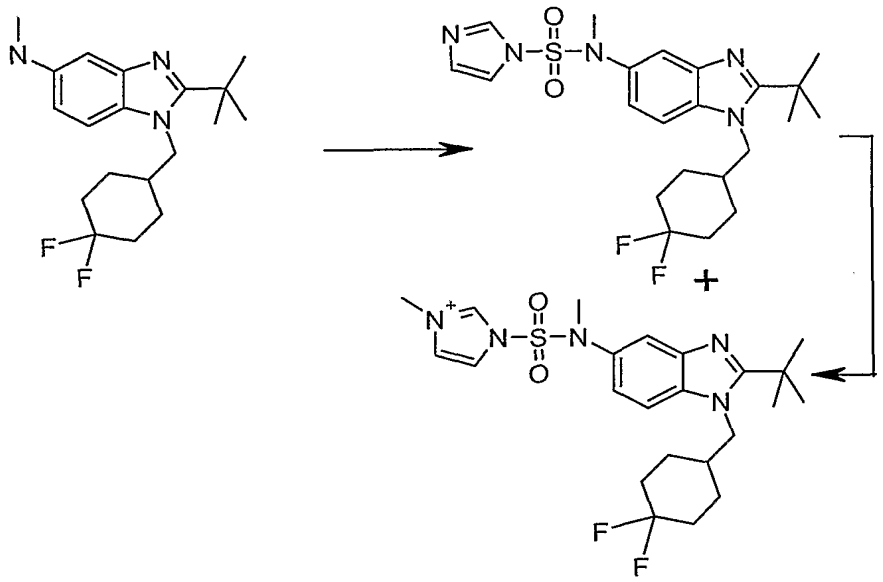
Step G. 2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine



N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylacetamide (570 mg, 1.51 mmol) and conc. hydrochloric acid (15 mL) were heated together at 80°C for 18 hrs. Upon cooling down to room temperature, the reaction mixture was poured into ice-water (100 mL), brought the pH to13 by using conc. NaOH and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and evaporation, 459 mg

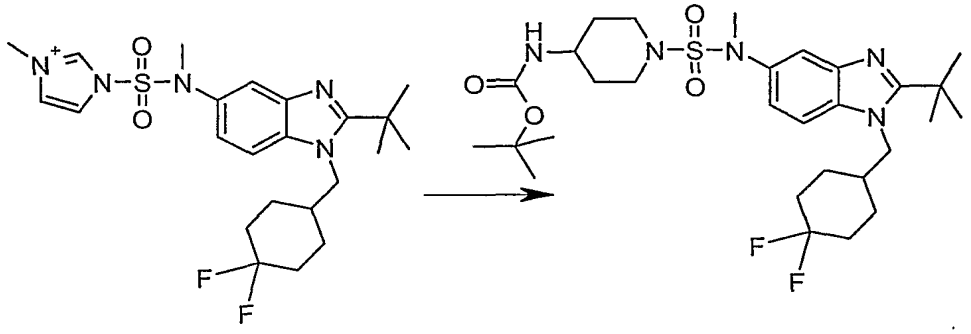
(90%) of the title compound was obtained as a white solid. MS (ESI) $(M+H)^+$: 336.04.

Step H: 1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate



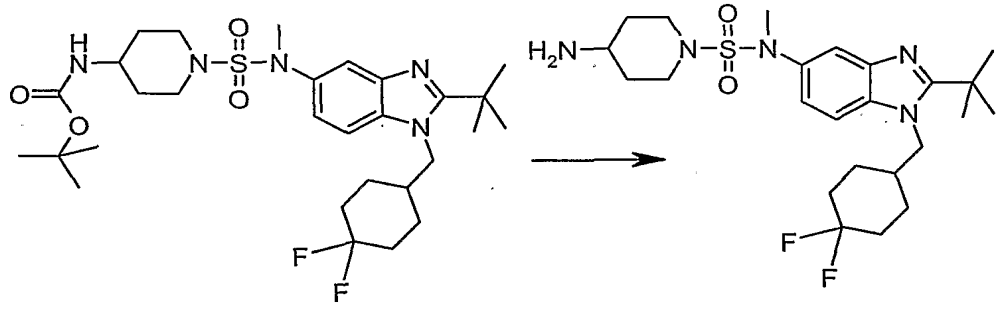
3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium triflate (508 mg; 1.4 mmol) was added into a solution of 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (300 mg, 0.9 mmol) in acetonitrile (10 mL). After being stirred at room temperature for 2 hr, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with brine, and dried over Na_2SO_4. Removal of solvents provided a mixture (1:1) of *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide and 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate, which was dissolved in dichloromethane (10 mL). The resulting solution was treated with methyl trifluoromethanesulfonate (0.5 mmol) at 0°C for 2 hr. The reaction mixture was then concentrated under reduced pressure to give 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate as a solid, which was used in the step I without any purification.

Step I: *tert*-Butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate



A solution of Hunig's base (1.0 mmol), 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (crude product from Step H, 0.9 mmol) and *tert*-butyl piperidin-4-ylcarbamate (200 mg, 1.0 mmol) in MeCN (20 mL) was heated for 1 hr at 80°C. The reaction mixture was then concentrated under reduced pressure to give crude *tert*-butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate as a solid, which was used directly in Step J.

Step J: 4-Amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide

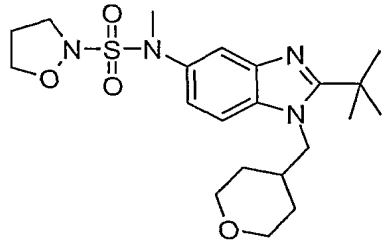


A solution of *tert*-butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate (crude product from Step I, 0.9 mmol) in 10 mL CH_2Cl_2 was treated with 10 mL TFA at room temperature. After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with Na_2CO_3 solution and brine, and dried over Na_2SO_4. Removal of solvents provided the crude 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-

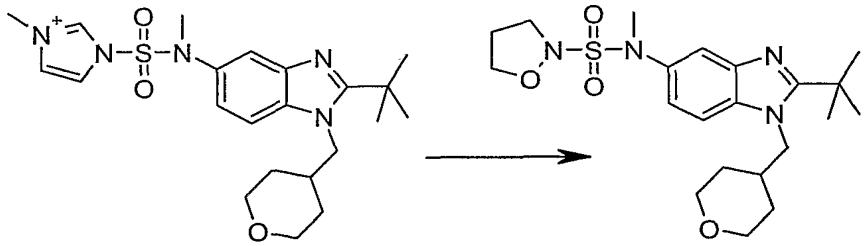
difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide, which was used in Step A without purification.

Example 2

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide

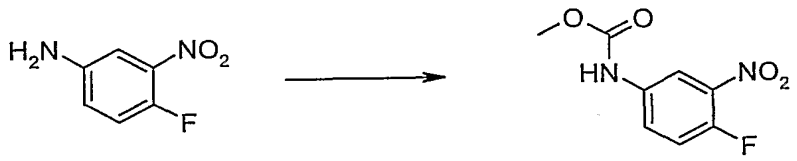


Step A: N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide



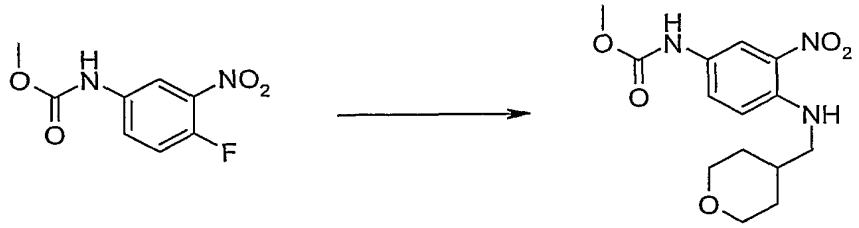
Following the procedure in Step I of Example 1, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (crude product from Step G, 1.67 mmol) was reacted with isoxazolidine hydrochloride (220 mg, 2.0 mmol) and Hunig's base (0.72 mL, 4.2 mml), after being purified by silica gel chromatography by using 20-30 % AcOEt in dichloromethane, to provide N-[2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide (TFA salt, 807 mg, 88 %): ^{1}H NMR (600 MHz, CD_3OD) δ 1.43-1.56 (m, 4H), 1.60 (s, 9H), 2.22-2.35 (m, 3H), 3.26 (t, J = 11.14Hz, 2H), 3.37 (s, 3H), 3.47 (t, J = 7.17Hz, 2H), 3.85 (dd, J = 11.26, 3.33Hz, 2H), 4.03 (t, J = 7.30Hz, 2H), 4.46 (d, J = 7.17Hz, 2H), 7.63 (dd, J = 8.70, 1.02Hz, 1H), 7.80-7.84 (d, J = 1.28Hz, 1H), 7.88 (d, J = 8.96Hz, 1H).

Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate



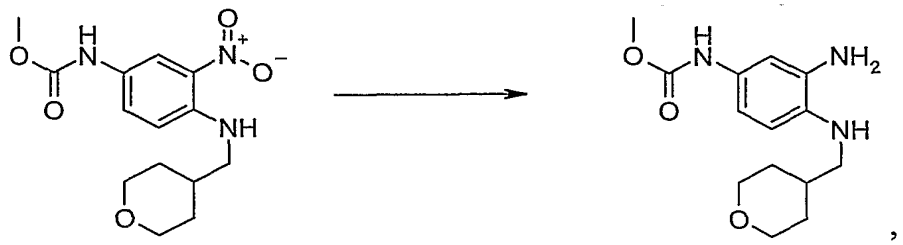
Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was directly used for next step without further purification. Yield: 35.5 g (99%); ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, J = 8.59Hz, 1H), 8.17 (dd, J = 6.35, 2.64Hz, 1H).

Step C. Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



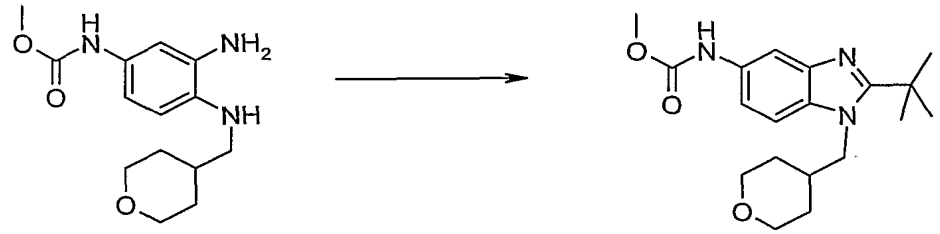
Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0 g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48 h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53 g (88%); ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.42 (m, 4.49 Hz, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (dd, *J*=6.74, 5.57 Hz, 2 H), 3.42 (m, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

Step D. Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53 g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through Celite and the solvent was evaporated. Yield: 2.29 g (99%); ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.40 (m, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (d, *J*=6.64 Hz, 2 H), 3.34 (br.s, 2 H), 3.41 (m, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

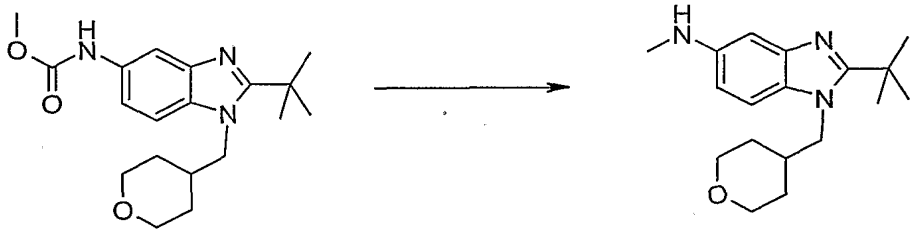
Step E. Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate



Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate (2.29 g, 8.20 mmol) and DMAP (0.20 g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The

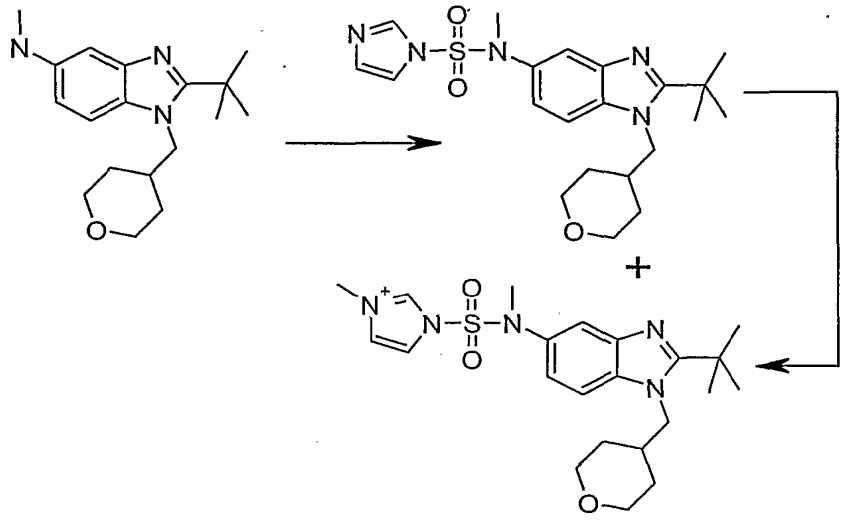
crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81 g (64%); ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.48 - 1.54 (m, 4 H) 1.56 (s, 9 H) 2.23 - 2.35 (m, 1 H) 3.27 - 3.35 (m, 2 H) 3.78 (s, 3 H) 3.96 (t, *J*=2.93 Hz, 1 H) 3.99 (t, *J*=3.03 Hz, 1 H) 4.18 (d, *J*=7.42 Hz, 2 H) 6.63 (br.s, 1 H) 7.24 - 7.28 (m, 1 H) 7.41 (br.s, 1 H) 7.61 (d, *J*=1.95 Hz, 1 H).

Step F: 2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



Methyl [2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80g, 5.21 mmol) (for preparation, see Steps B to E) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min. Anhydrous Na_2SO_4 (10 g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 1.54g (98%); ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

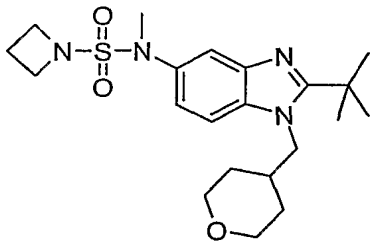
Step G: 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate.



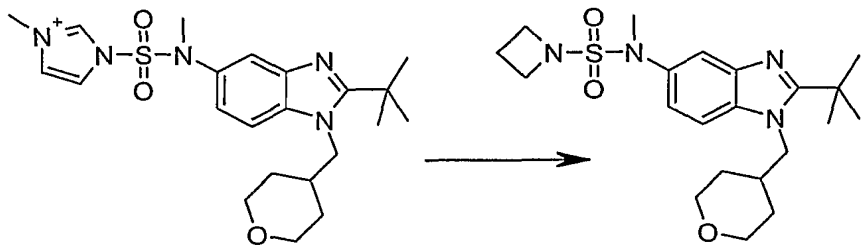
Following the procedure in Step H of Example 1, 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (1.51 g, 5.0 mmol) was converted to 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate, which was used in Step A without any purification.

Example 3

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide



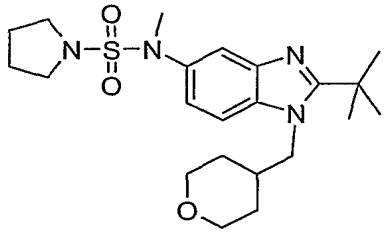
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl) -1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide**



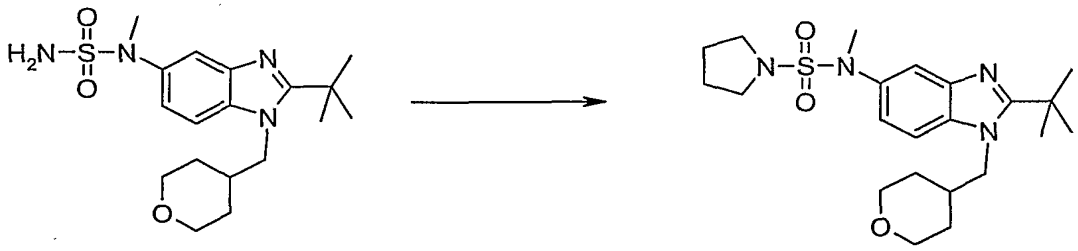
Following the procedure in Step A of Example 2, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (3.33 mmol) was reacted with trimethlene amine (4.99 mmol), after being purified by silica gel chromatography by using 20-50 % AcOEt in dichloromethane, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (TFA salt, 675 mg, 38 %). MS (M+1): 421.01. ^{1}H NMR (600 MHz, CD_3OD) δ 1.40-1.53 (m, 4H), 1.57 (s, 9H), 2.14 (quint, J = 7.68Hz, 2H), 2.23-2.33 (m, 1H), 3.22 (s, 3H), 3.25 (m, 2H), 3.80 (t, J = 7.68Hz, 4H), 3.84 (m, 2H), 4.41 (d, J = 7.42Hz, 2H), 7.51 (d, J = 8.70Hz, 1H), 7.67 (d, J = 1.79Hz, 1H), 7.80 (d, J = 8.45Hz, 1H).

Example 4

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide**



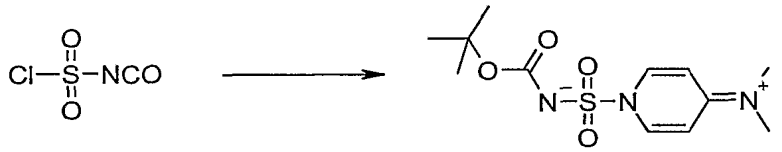
Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide



N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylsulfamide (for preparation see the following steps B to H) (45 mg, 0.118 mmol) was dissolved in 5 mL of DMF at 0°C. NaH (60% dispersion in oil) (14 mg, 0.354 mmol) was added and the solution was stirred at 0°C for 10 min. 1,4-Dibromobutane (0.014 mL, 0.118 mmol) was added and the solution was stirred at rt

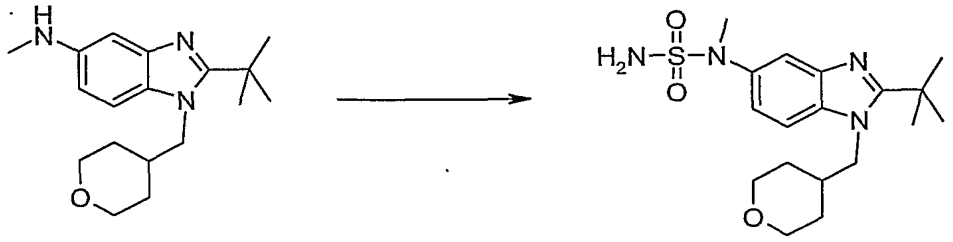
for 3h. Another 0.118 mmol of 1,4-dibrombutane was added and the solution was stirred at rt for another 3h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 53 mg (82%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.52 - 1.58 (m, 2 H), 1.59 - 1.67 (m, 2 H), 1.69 (s, 9 H), 1.87 - 1.92 (m, 4 H), 2.35 - 2.43 (m, 1 H), 3.29 - 3.32 (m, 7 H), 3.35 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.55 (d, J=7.42 Hz, 2 H), 7.67 (dd, J=8.98, 1.95 Hz, 1 H), 7.81 (d, J=2.15 Hz, 1 H), 7.97 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 435.0; Anal. Calcd(%) for $C_{22}H_{34}N_4O_3S$ + 2.4 TFA + 0.2 H_2O: C, 45.22; H, 5.21; N, 7.87. Found: C, 45.20; H, 5.27; N, 7.90.

Step B: (*tert*-Butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide



Chlorosulfonyl isocyanate (1.2 mL, 13.8 mmol) was added dropwise to a stirring DCM solution (10 mL) of t-butanol (1.3 mL, 13.8 mmol). DMAP (3.45g, 27.6 mmol) was added slowly and the solution was stirred at rt for 2h. The solution was diluted with DCM and washed with water (3X), brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The product was recrystallized from acetonitrile. Yield (1.68g (40%). ^1H NMR (400 MHz, DMSO-D_6) δ 1.25 (s, 9 H), 3.21 (s, 6 H), 6.96 (d, J=8.20 Hz, 2 H), 8.45 (d, J=8.01 Hz, 2 H).

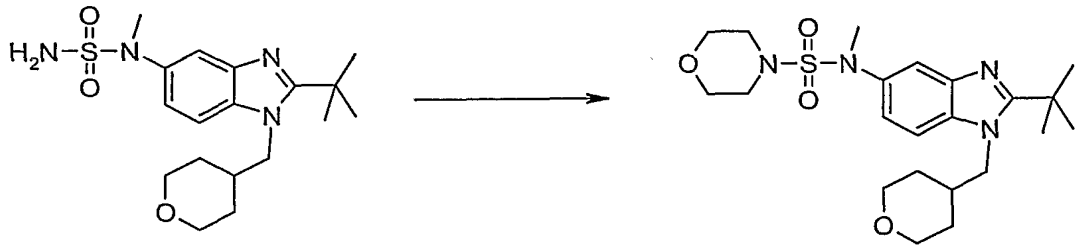
Step C: N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylsulfamide



2-tert-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine (60 mg, 0.199mmol) (for preparation, see Example 2, Steps B to F) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (66 mg, 0.219 mmol) were stirred in 3 mL of DCE at 70°C for 2h. The solution was then passed through a plug of silica gel using EtOAc as eluent. The solvent was evaporated. The residue was dissolved in 3 mL of 1M HCl/AcOH and the solution was stirred at rt for 1h. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and then lyophilized affording the title compound as the corresponding TFA salt. The fractions were pooled and the solvent was concentrated. The residue was dissolved in 2M Na_2CO_3 and extracted with DCM (3X). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was evaporated. Yield: 45 mg (59%). ^{1}H NMR (TFA salt) (400 MHz, METHANOL-D_4) δ 1.50 - 1.56 (m, 2 H), 1.57 - 1.62 (m, 2 H), 1.67 (s, 9 H), 2.33 - 2.42 (m, 1 H), 3.28 (s, 3 H), 3.34 (m, 2 H), 3.93 (m, 2 H), 4.53 (d, J=7.62 Hz, 2 H), 7.64 (dd, J=8.98, 1.95 Hz, 1 H), 7.77 (d, J=1.56 Hz, 1 H), 7.91 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 381.0.

Example 5

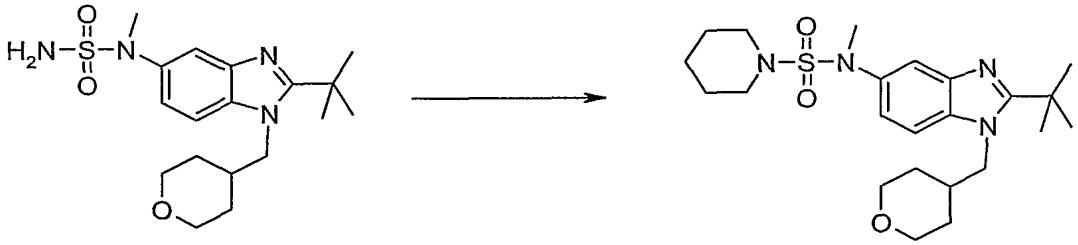
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylmorpholine-4-sulfonamide**



Following Step A in Example 4 using N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylsulfamide (45 mg, 0.118 mmol), NaH (14 mg, 0.354 mmol) and 2-bromoethyl ether (0.030 mL, 0.236 mmol) in 4 mL of DMF. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 42 mg (63%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.52 - 1.58 (m, 2 H), 1.59 - 1.66 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.43 (m, 1 H), 3.20 - 3.24 (m, 4 H), 3.32 - 3.40 (m, 5 H), 3.63 - 3.67 (m, 4 H), 3.93 (d, J=3.32 Hz, 1 H), 3.96 (d, J=3.71 Hz, 1 H), 4.54 (d, J=7.42 Hz, 2 H), 7.69 (dd, J=8.98, 1.95 Hz, 1 H), 7.82 (d, J=1.76 Hz, 1 H), 7.96 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 451.0; Anal. Calcd(%) for $C_{22}H_{34}N_4O_4S$ + 1.2 TFA + 1.0 H_2O: C, 48.41; H, 6.19; N, 9.25. Found: C, 48.29; H, 6.00; N, 9.53.

Example 6

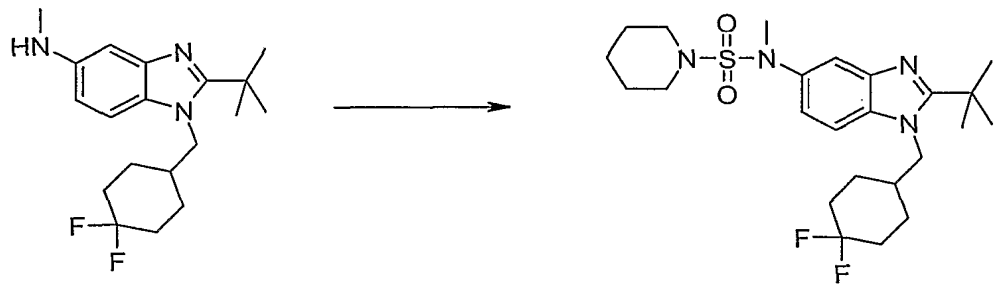
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperidine-1-sulfonamide**



Following Step A in Example 4 using N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylsulfamide (40 mg, 0.105 mmol), NaH (13 mg, 0.315 mmol) and 1,5-dibromopentane (0.042 mL, 0.315 mmol) in 4 mL of DMF. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 42 mg (71%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.52 - 1.60 (m, 8 H), 1.59 - 1.67 (m, 2 H), 1.69 (s, 9 H), 2.34 - 2.43 (m, 1 H), 3.20 - 3.25 (m, 4 H), 3.31 (s, 3 H), 3.35 (m, 2 H), 3.93 (d, J=3.12 Hz, 1 H), 3.96 (d, J=3.91 Hz, 1 H), 4.54 (d, J=7.62 Hz, 2 H), 7.67 (dd, J=8.98, 1.95 Hz, 1 H), 7.80 (d, J=1.76 Hz, 1 H), 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 449.0; Anal. Calcd(%) for $C_{23}H_{36}N_4O_3S$ + 1.3 TFA + 0.9 H_2O: C, 50.15; H, 6.43; N, 9.14. Found: C, 50.22; H, 6.52; N, 9.10.

Example 7

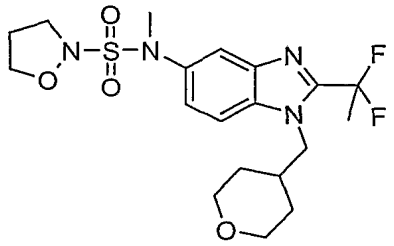
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide**



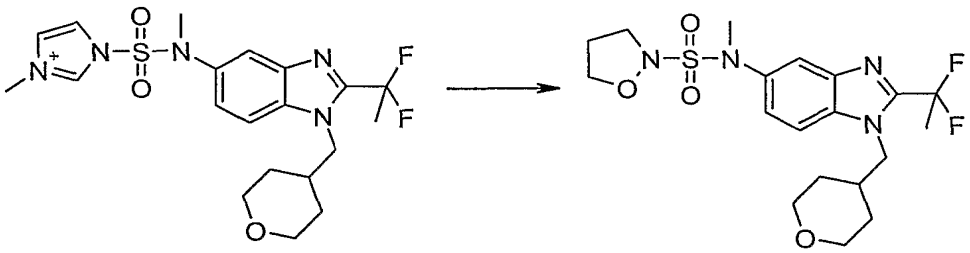
2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (55 mg, 0.164 mmol) (for preparation, see Example 1, Steps B to G) and (*tert*-butoxycarbonyl){[4-(dimethyliminio)pyridin-1(4*H*)-yl]sulfonyl}azanide (54 mg, 0.180 mmol) were stirred in 3 mL of DCE at 70°C for 2h. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc to EtOAc as a gradient. The resulting product was dissolved in 3 mL of 1M HCl/AcOH and stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The product was dissolved in 3 mL of DMF at 0°C and NaH (20 mg, 0.492 mmol) was added, followed by 1,5-dibromopentane (0.033 mL, 0.246 mmol). The solution was stirred at rt for 2h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-60% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 15 mg (15%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.54 - 1.61 (m, 8 H), 1.68 (s, 9 H), 1.71 - 1.85 (m, 4 H), 2.01 - 2.12 (m, 2 H), 2.21 - 2.33 (m, 1 H), 3.20 - 3.25 (m, 4 H), 3.31 (s, 3 H), 4.56 (d, *J*=7.62 Hz, 2 H), 7.67 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.81 (d, *J*=2.15 Hz, 1 H), 7.94 (d, *J*=9.18 Hz, 1 H); MS (ESI) $(M+H)^+$ 483.0; Anal. Calcd(%) for $C_{24}H_{36}N_4O_2SF_2$ + 1.8 TFA + 0.4 H_2O: C, 47.69; H, 5.60; N, 8.06. Found: C, 47.66; H, 5.58; N, 8.07.

Example 8

***N*-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylisoxazolidine-2-sulfonamide**

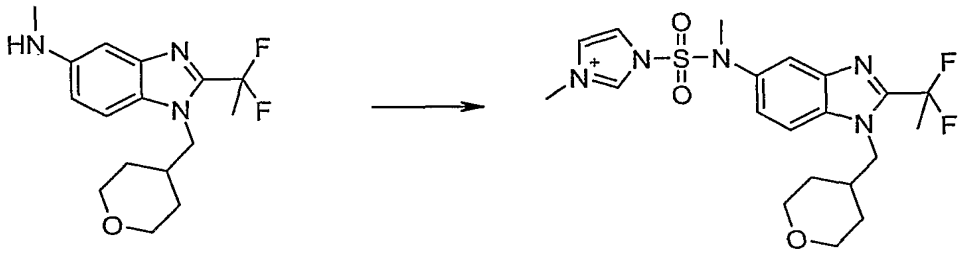


Step A. *N*-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylisoxazolidine-2-sulfonamide



Isoxazolidin-2-ium chloride (80 mg, 0.72 mmol) and DIPEA (0.12 mL, 0.72 mmol) were added to the reaction mixture (18 mL) prepared in step B in this example. The resulting reaction mixture was heated to 60°C overnight and the solvent was concentrated. . The product was purified by reverse-phase preparative HPLC using MeCN 10 to 90% gradient in water to provide the TFA salt of the title compound as white solid. Yield: 50 mg (18%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.38 - 1.51 (m, 4 H), 2.21 (t, J=19.34 Hz, 3 H), 2.28 - 2.39 (m, 2 H), 3.29 - 3.35 (m, 2 H), 3.41 (s, 3 H), 3.53 (dd, J=8.01, 6.64 Hz, 2 H), 3.84 - 3.93 (m, 2 H), 4.12 (t, J=7.42 Hz, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 7.51 (dd, J=8.89, 2.05 Hz, 1 H), 7.66 (d, J=8.98 Hz, 1 H), 7.83 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ 445.0; Anal. Calcd for $C_{19}H_{26}F_2N_4O_4S$ + 0.3 TFA + 0.1 H_2O: C, 48.99; H, 5.56; N, 11.16. Found: C, 49.02; H, 5.60; N, 11.67.

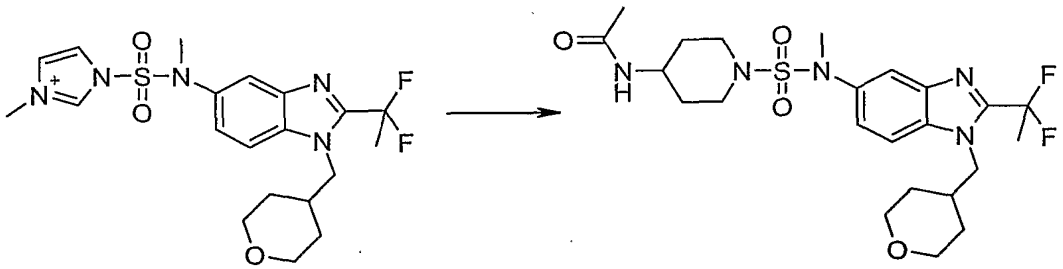
Step B. 1-{[[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium



1-(1*H*-Imidazol-1-ylsulfonyl)-3-methyl-1*H*-imidazol-3-ium difluoromethanesulfonate (1.05 g, 2.90 mmol) was added to a solution of 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (0.60 g, 1.93 mmol) in MeCN (70 mL) at ambient temperature. The reaction mixture was stirred for 4 hrs. and methyl trifluoromethyl sulfone (0.21 mL, 1.93 mmol) was added. The reaction mixture was stirred for 2hrs and used directly for the next step.

Example 9

***N*-(1-{[[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide**

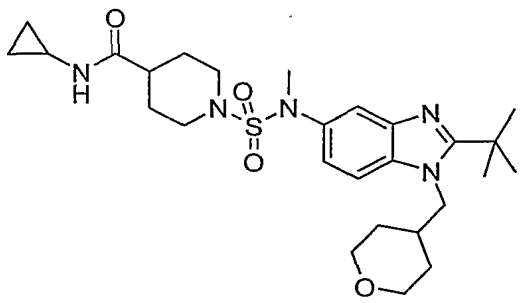


tert-Butyl piperidin-4-ylcarbamate (0.43 mg, 1.45 mmol) was added to the reaction mixture (52 mL) prepared in example 1, step B. The resulting reaction mixture was heated to 90°C overnight. *tert*-Butyl piperidin-4-ylcarbamate (0.43 mg, 1.45 mmol) was added again and the reaction mixture was heated to 90°C overnight. The solvent was concentrated and DCM (50 mL) was added to the residue. The resulting precipitate was filtered and air-dried to provide 404 mg of *tert*-butyl (1-{[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)carbamate intermediate. The solid was treated with TFA (10 mL) for 1.5 hr. and the solvent was concentrated. The resulting 4-amino-*N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-

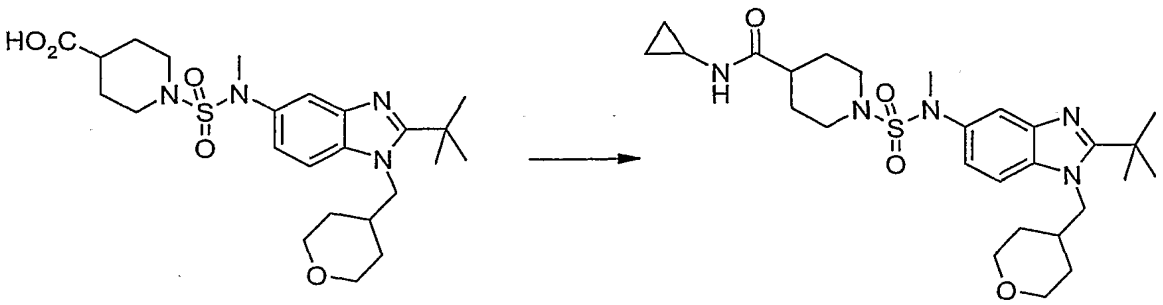
benzimidazol-5-yl]-*N*-methylpiperidine-1-sulfonamide TFA salt intermediate was dissolved in DCM (100 mL) and the solution was neutralized with Et_3N (2 mL) at 0°C. Acetyl chloride (10 drops) was added to the solution at 0°C, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. The solvent was concentrated and the product was purified by reverse-phase preparative HPLC using MeCN 10 to 90% gradient in water to provide the TFA salt of the title compound as white solid. Yield: 160 mg (21%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.35 - 1.54 (m, 6 H), 1.78 - 1.87 (m, 2 H), 1.90 (s, 3 H), 2.24 (t, J=19.33 Hz, 3 H), 2.30 (s, 1 H), 2.83 - 2.94 (m, 2 H), 3.27 - 3.30 (m, 3 H), 3.30 - 3.38 (m, 2 H), 3.60 - 3.77 (m, 4 H), 3.86 - 3.96 (m, 2 H), 4.35 (d, J=7.62 Hz, 2 H), 7.51 (dd, J=8.79, 2.15 Hz, 1 H), 7.71 (d, J=8.98 Hz, 1 H), 7.79 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ 514.0; Anal. Calcd for $C_{23}H_{33}F_2N_5O_4S$ + 0.7 TFA + 0.2 H_2O: C, 49.09; H, 5.76; N, 11.73. Found: C, 49.06; H, 5.69; N, 11.68.

Example 10

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperidine-4-carboxamide

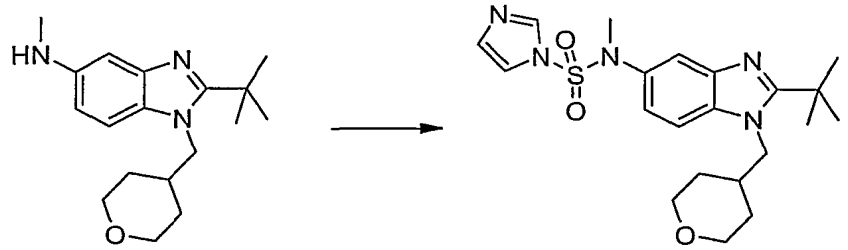


Step A. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperidine-4-carboxamide



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.142 mmol, see Steps B to E for its preparation), diisopropylethylamine (0.029 mL, 0.170 mmol), and cyclopropylamine (30 μL, excess) at room temperature in DMF (3 mL), was added HATU (64.6 mg, 0.170 mmol) in one portion. The solution was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-60% CH_3CN in H_2O) to provide the title compound as its TFA salt (29.1 mg, 32%). ^1H NMR (400 MHz, $CDCl_3$) δ 0.47 - 0.54 (m, 2 H), 0.69 - 0.77 (m, 2 H), 1.52 - 1.70 (m, 6 H), 1.73 (s, 9 H), 1.75 - 1.82 (m, 2 H), 2.13 - 2.24 (m, 1 H), 2.26 - 2.39 (m, 1 H), 2.65 - 2.71 (m, 1 H), 2.71 - 2.81 (m, 2 H), 3.31 (s, 3 H), 3.32 - 3.41 (m, 2 H), 3.57 - 3.65 (m, 2 H), 4.00 - 4.07 (m, 2 H), 4.38 (d, J=7.42 Hz, 2 H), 6.43 - 6.48 (m, 1 H), 7.55 (d, J=8.98 Hz, 1 H), 7.66 (dd, J=8.98, 1.37 Hz, 1 H), 7.90 - 7.93 (m, 1 H); MS (ESI) $(M+H)^+$ 532.0; Anal. (C, H, N) calcd for $C_{27}H_{41}N_5O_4S$+2.30CF_3COOH: C 47.80, H 5.50, N 8.82; found C 47.93, H 5.22, N 8.91.

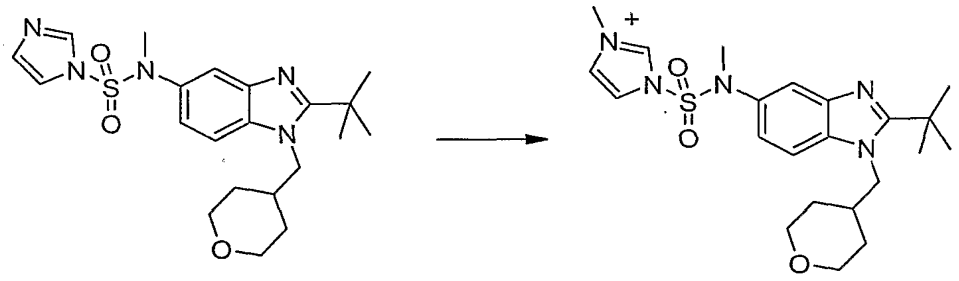
Step B. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-1*H*-imidazole-1-sulfonamide



To a solution of 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (1.97 g, 6.54 mmol) at room temperature in MeCN (40 mL),

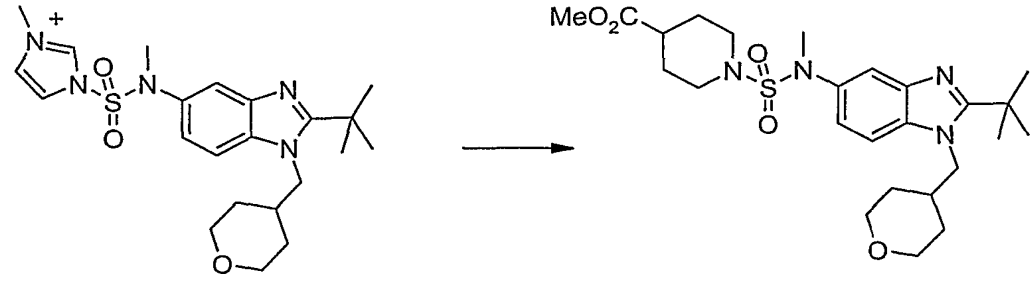
was added 1-(1*H*-imidazol-1-ylsulfonyl)-3-methyl-1*H*-imidazol-3-ium (3.6g, 9.81 mmol) in one portion. The solution was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by flash chromatography (0-100% EtOAc in hexanes, 50min; 100% EtOAc, 10min; 0-2% MeOH in EtOAc, 10min) to afford the product (1.24 g, 44%). MS (ESI) $(M+H)^+$ 432.0.

Step C. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium



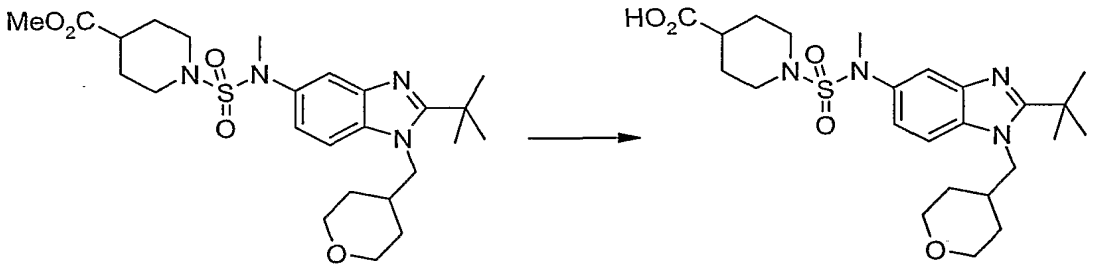
To a solution of *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-1*H*-imidazole-1-sulfonamide (1.24 g, 2.88 mmol) at room temperature in MeCN (20 mL), was added methyl trifluoromethanesulfonate (0.49 mL, 4.32 mmol) dropwise. The solution was stirred at room temperature for 5 hours. After evaporation of the solvent, the residue was used directly for the next step without purification (1.0 g, 76%). MS (ESI) $(M+H)^+$ 446.0.

Step D. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (1 g, 2.2 mmol) and diisopropylethylamine (0.38 mL, 2.2 mmol) at room temperature in MeCN (15 mL), was added methyl isonipecotate (0.61 mL, 4.5 mmol) in one portion. The solution was stirred at room temperature overnight. After evaporation of the solvent, the residue was purified by flash chromatography (0-100% EtOAc in hexanes, 50min; 100% EtOAc, 10min; 0-2% MeOH in EtOAc, 10min) to provide the title compound (1.08 g, 97%). MS (ESI) $(M+H)^+$ 507.0.

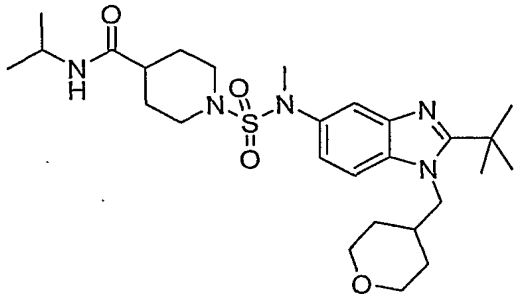
Step E. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid



To a solution of methyl 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate (1.08 g, 2.13 mmol) at 0°C in MeOH:H_2O (3:1, 20 mL), was added LiOH (178.5 mg, 7.46 mmol) in one portion. The solution was stirred at 0°C, slowly warmed to room temperature and stirred at room temperature overnight. The solution was adjusted to pH 2 with 1N HCl (12 mL), the aqueous layer was extracted with DCM. The organic layers were dried over Na_2SO_4, and subjected to filtration. Evaporation of the solvent provided the title compound (2.2 g, 92%). MS (ESI) $(M+H)^+$ 493.0.

Example 11

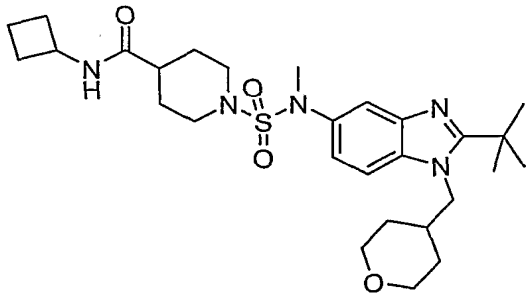
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (200 mg, 0.41 mmol), diisopropylethylamine (0.17 mL, 0.96 mmol), isopropylamine (0.11 mL, 1.22 mmol), DMF (6 mL), and HATU (182.6 mg, 0.48 mmol) provided the title compound as its TFA salt (150 mg, 57 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J=6.64 Hz, 6 H) 1.52 - 1.70 (m, 6 H) 1.72 (s, 9 H) 1.76 - 1.84 (m, 2 H) 2.13 - 2.23 (m, 1 H) 2.27 - 2.40 (m, 1 H) 2.71 - 2.85 (m, 2 H) 3.32 (s, 3 H) 3.34 - 3.41 (m, 2 H) 3.62 - 3.72 (m, 2 H) 3.98 - 4.09 (m, 3 H) 4.37 (d, J=7.42 Hz, 2 H) 5.97 (d, J=7.62 Hz, 1 H) 7.54 (d, J=8.98 Hz, 1 H) 7.68 (dd, J=8.98, 1.76 Hz, 1 H) 7.89 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ 534.0; Anal. (C, H, N) calcd for $C_{27}H_{43}N_5O_4S$+2.00CF_3COOH+0.10CH_3OH: C 48.83, H 5.98, N 9.15; found C 48.83, H 5.93, N 9.07.

Example 12

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperidine-4-carboxamide

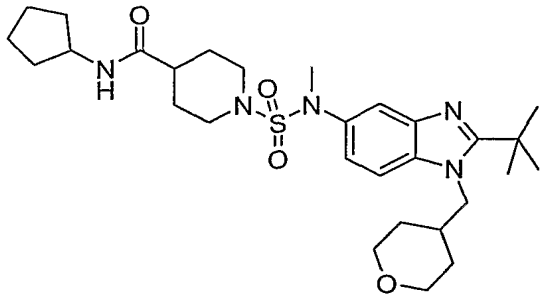


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-

yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), cyclobutylamine (0.030 mL, excess), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (37.8 mg, 40 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 - 1.71 (m, 10 H), 1.72 (s, 9 H), 1.77 - 1.95 (m, 3 H), 2.12 - 2.23 (m, 1 H), 2.23 - 2.39 (m, 3 H), 2.74 - 2.85 (m, 2 H), 3.33 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.66 (d, J=15.04 Hz, 2 H), 4.04 (d, J=10.94 Hz, 2 H), 4.37 (d, J=7.42 Hz, 2 H), 6.35 (d, J=8.01 Hz, 1 H), 7.53 (d, J=8.98 Hz, 1 H), 7.69 (dd, J=9.08, 1.86 Hz, 1 H), 7.90 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ 546.0; Anal. (C, H, N) calcd for $C_{28}H_{43}N_5O_4S$+2.10CF_3COOH: C 49.26, H 5.79, N 8.92; found C 49.21, H 5.65, N 9.07.

Example 13

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperidine-4-carboxamide

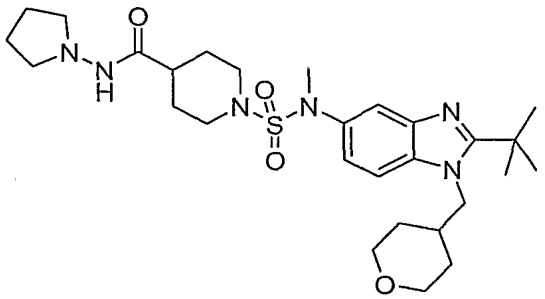


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), cyclopentylamine (0.030 mL, excess), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (37.8 mg, 40 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 - 1.42 (m, 2 H), 1.52 - 1.69 (m, 10 H), 1.72 (s, 9 H), 1.76 - 1.85 (m, 3 H), 1.89 - 2.01 (m, 2 H), 2.75 - 2.86 (m, 2 H), 3.34 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.65 - 3.73 (m, 2 H), 4.00 - 4.07 (m, 2 H), 4.11 - 4.21 (m, 1 H), 4.36 (d, J=6.84 Hz, 2 H), 7.52 (d, J=8.79 Hz, 1 H), 7.67 - 7.73 (m, J=7.81 Hz, 1 H), 7.91 - 7.95 (m, 1 H); MS (ESI) $(M+H)^+$ 560.0; Anal. (C, H, N) calcd

for $C_{29}H_{45}N_5O_4S$+1.70CF_3COOH+0.20H_2O +0.40CH_3OH: C 51.16, H 6.37, N 9.09; found C 51.15, H 6.34, N 9.00.

Example 14

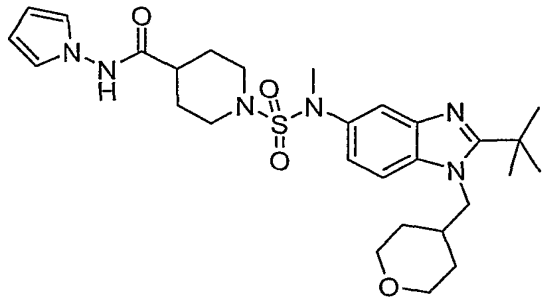
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-pyrrolidin-1-ylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), 1-aminopyrrolidine hydrochloride (20.8 mg, 0.17 mmol), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (37.8 mg, 40 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 - 1.70 (m, 7 H), 1.72 (s, 9 H), 1.74 - 1.84 (m, 2 H), 2.12 - 2.23 (m, 4 H), 2.37 - 2.48 (m, 1 H), 2.87 - 3.00 (m, 3 H), 3.33 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.44 - 3.53 (m, 2 H), 3.65 - 3.74 (m, 4 H), 3.99 - 4.07 (m, 2 H), 4.38 (d, J=7.42 Hz, 2 H), 7.57 (d, J=8.89 Hz, 1 H), 7.69 (dd, J=8.89, 2.05 Hz, 1 H), 7.88 (d, J=2.05 Hz, 1 H); MS (ESI) $(M+H)^+$ 561.0; Anal. (C, H, N) calcd for $C_{28}H_{44}N_6O_4S$+2.75CF_3COOH+0.55H_2O +0.15CH_3OH: C 45.46, H 5.49, N 9.45; found C 45.47, H 5.49, N 9.46.

Example 15

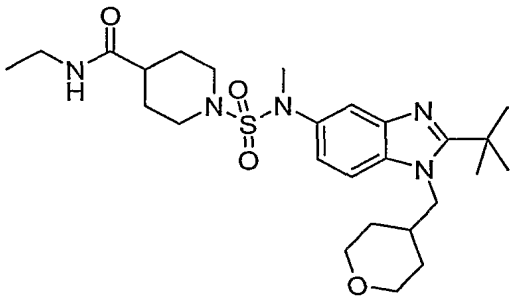
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-1*H*-pyrrol-1-ylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), 1-aminopyrrole (0.030 mL, excess), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (37.8 mg, 40 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 - 1.63 (m, 4 H), 1.71 (s, 9 H), 1.72 - 1.95 (m, 2 H), 2.26 - 2.50 (m, 2 H), 2.75 - 2.86 (m, 2 H), 3.23 - 3.41 (m, 6 H), 3.58 - 3.72 (m, 3 H), 3.96 - 4.08 (m, 2 H), 4.37 (d, J=7.42 Hz, 2 H), 6.06 - 6.15 (m, 2 H), 6.56 - 6.61 (m, 2 H), 7.56 (d, J=9.18 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.91 (d, J=1.17 Hz, 1 H); MS (ESI) $(M+H)^+$ 557.0; Anal. (C, H, N) calcd for $C_{28}H_{40}N_6O_4S+1.75CF_3COOH+0.35CH_3OH$: C 49.85, H 5.67, N 10.95; found C 49.97, H 5.61, N 10.84.

Example 16

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperidine-4-carboxamide

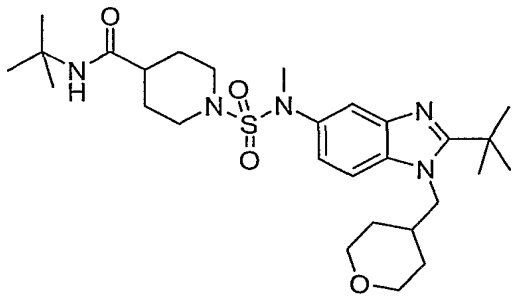


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol),

diisopropylethylamine (0.029 mL, 0.17 mmol), ethylamine (0.21 mL, 0.43 mmol), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (41.5 mg, 46 %) following purification by reversed-phase HPLC (10-65% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.13 Hz, 3 H), 1.51 - 1.69 (m, 6 H), 1.72 (s, 9 H), 1.75 - 1.86 (m, 2 H), 2.19 - 2.41 (m, 2 H), 2.70 - 2.82 (m, 2 H), 3.21 - 3.28 (m, 2 H), 3.30 (s, 3 H), 3.31 - 3.41 (m, 2 H), 3.56 - 3.67 (m, 2 H), 3.98 - 4.08 (m, 2 H), 4.39 (d, J=7.42 Hz, 2 H), 6.47 - 6.56 (m, 1 H), 7.56 - 7.62 (m, 1 H), 7.63 - 7.69 (m, 1 H), 7.87 (s, 1 H); MS (ESI) $(M+H)^+$ 520.0; Anal. (C, H, N) calcd for $C_{26}H_{41}N_5O_4S$+2.35CF_3COOH: C 46.81, H 5.55, N 8.89; found C 46.49, H 5.09, N 9.32.

Example 17

***N*-(*tert*-Butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide**

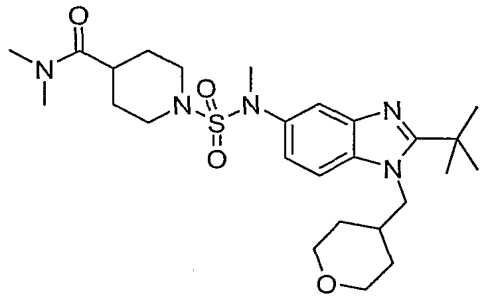


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), *t*-butylamine (0.045 mL, 0.43 mmol), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (44.2 mg, 47 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9 H), 1.52 - 1.70 (m, 6 H), 1.71 (s, 9 H), 1.73 - 1.81 (m, 2 H), 2.05 - 2.18 (m, 1 H), 2.26 - 2.40 (m, 1 H), 2.69 - 2.81 (m, 2 H), 3.31 (s, 3 H), 3.32 - 3.42 (m, 2 H), 3.63 - 3.71 (m, 2 H), 3.99 - 4.07 (m, 2 H), 4.38 (d, J=7.42 Hz, 2 H), 5.79 - 5.85 (m, 1 H), 7.57 (d, J=8.98 Hz, 1 H), 7.68 (dd, J=8.98, 1.37 Hz, 1 H), 7.82 - 7.86 (m, 1 H); MS (ESI) $(M+H)^+$ 548.0; Anal. (C,

H, N) calcd for $C_{28}H_{45}N_5O_4S$+2.10CF_3COOH+1.25H_2O: C 47.76, H 6.17, N 8.65; found C 47.45, H 5.88, N 8.96.

Example 18

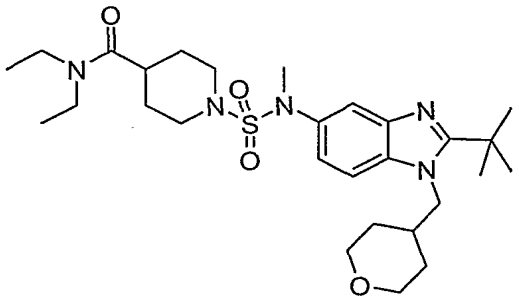
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 μL, 0.17 mmol), *N*,*N*-dimethylamine (0.21 mL, 0.43 mmol), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (33.7 mg, 37 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 - 1.65 (m, 5 H), 1.65 - 1.79 (m, 12 H), 2.25 - 2.40 (m, 1 H), 2.63 - 2.75 (m, 1 H), 2.84 - 2.92 (m, 2 H), 2.93 (s, 3 H), 3.06 (s, 3 H), 3.32 (s, 3 H), 3.33 - 3.41 (m, 2 H), 3.68 - 3.77 (m, 2 H), 3.98 - 4.08 (m, 2 H), 4.37 (d, J=7.42 Hz, 2 H), 7.54 (d, J=8.98 Hz, 1 H), 7.68 (dd, J=8.98, 0.98 Hz, 1 H), 7.89 - 7.93 (m, 1 H); MS (ESI) $(M+H)^+$ 520.0; Anal. (C, H, N) calcd for $C_{26}H_{41}N_5O_4S$+1.80CF_3COOH+0.75H_2O: C 48.14, H 6.05, N 9.48; found C 48.09, H 6.00, N 9.57.

Example 19

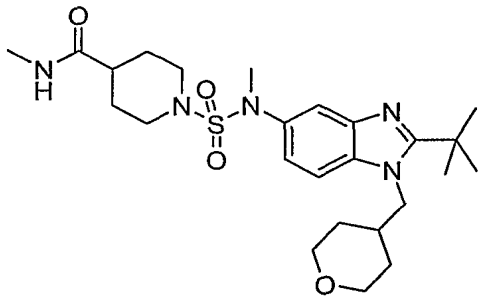
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-diethylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), *N,N*-diethylamine (0.044 mL, 0.43 mmol), DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (12.1 mg, 13 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J=7.13 Hz, 3 H), 1.19 (t, J=7.03 Hz, 3 H), 1.52 - 1.62 (m, 4 H), 1.65 - 1.69 (m, 1 H), 1.72 (s, 9 H), 1.72 - 1.87 (m, 3 H), 2.54 - 2.64 (m, 1 H), 2.86 - 2.96 (m, 2 H), 3.28 - 3.40 (m, 10 H), 3.71 - 3.80 (m, 2 H), 3.99 - 4.07 (m, 2 H), 4.35 (d, J=7.42 Hz, 2 H), 7.49 (d, J=8.98 Hz, 1 H), 7.70 (dd, J=8.98, 1.76 Hz, 1 H), 7.93 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ 548.0.

Example 20

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperidine-4-carboxamide

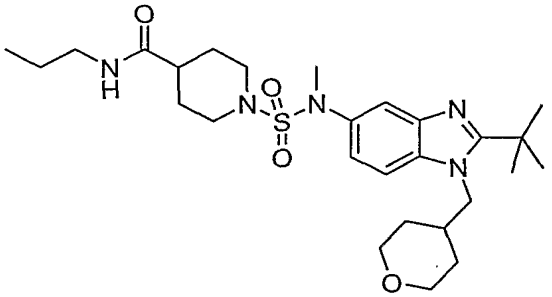


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.029 mL, 0.17 mmol), methylamine (0.21 mL, 0.43 mmol),

DMF (3 mL), and HATU (64.6 mg, 0.17 mmol) provided the title compound as its TFA salt (22.9 mg, 26 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.57 (d, 4 H), 1.65 - 1.76 (m, 12 H), 1.81 - 1.90 (m, 3 H), 2.79 (d, J=4.49 Hz, 3 H), 2.80 - 2.87 (m, 2 H), 3.33 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.61 - 3.69 (m, 2 H), 3.99 - 4.08 (m, 2 H), 4.36 (d, J=7.42 Hz, 2 H), 7.52 (d, J=9.18 Hz, 1 H), 7.70 (dd, J=9.18, 1.66 Hz, 1 H), 7.96 - 7.99 (m, 1 H); MS (ESI) $(M+H)^+$ 506.0; Anal. (C, H, N) calcd for $C_{25}H_{39}N_5O_4S+1.90CF_3COOH+0.20H_2O+0.25CH_3OH$: C 47.54, H 5.81, N 9.54; found C 47.54, H 5.82, N 9.53.

Example 21

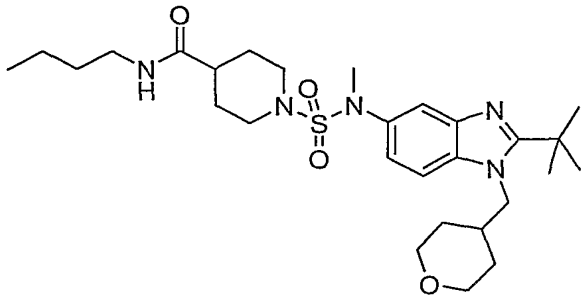
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.074 mL, 0.43 mmol), *N,N*-diethylamine (0.035 mL, 0.43 mmol), DMF (3 mL), and HATU (81 mg, 0.21 mmol) provided the title compound as its TFA salt (31.1 mg, 34 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, J=7.42 Hz, 3 H), 1.44 - 1.71 (m, 8 H), 1.72 (s, 9 H), 1.75 - 1.87 (m, 2 H), 2.17 - 2.41 (m, 2 H), 2.72 - 2.85 (m, 2 H), 3.14 - 3.23 (m, 2 H), 3.32 (s, 3 H), 3.33 - 3.42 (m, 2 H), 3.59 - 3.70 (m, 2 H), 3.98 - 4.09 (m, 2 H), 4.38 (d, J=7.42 Hz, 2 H), 6.30 - 6.42 (m, 1 H), 7.55 (d, J=8.98 Hz, 1 H), 7.68 (dd, J=8.98, 1.76 Hz, 1 H), 7.91 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ 534.0; Anal. (C, H, N) calcd for $C_{27}H_{43}N_5O_4S+1.80CF_3COOH+0.90CH_3OH$: C 49.28, H 6.29, N 9.06; found C 49.25, H 6.29, N 9.06.

Example 22

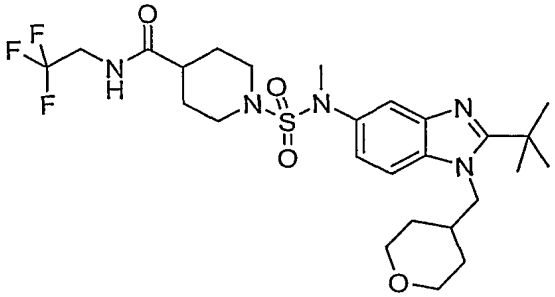
***N*-Butyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide**



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol), diisopropylethylamine (0.074 mL, 0.43 mmol), *N,N*-butylamine (42 μL, 0.43 mmol), DMF (3 mL), and HATU (81 mg, 0.21 mmol) provided the title compound as its TFA salt (31.1 mg, 34 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.32 Hz, 3 H), 1.24 - 1.39 (m, 2 H), 1.41 - 1.52 (m, 2 H), 1.52 - 1.70 (m, 6 H), 1.72 (s, 9 H), 1.77 - 1.87 (m, 2 H), 2.15 - 2.41 (m, 2 H), 2.74 - 2.87 (m, 2 H), 3.16 - 3.26 (m, 2 H), 3.32 (s, 3 H), 3.33 - 3.41 (m, 2 H), 3.60 - 3.72 (m, 2 H), 3.98 - 4.08 (m, 2 H), 4.37 (d, J=7.42 Hz, 2 H), 6.18 - 6.30 (m, 1 H), 7.54 (d, J=8.98 Hz, 1 H), 7.67 (dd, J=8.98, 1.76 Hz, 1 H), 7.94 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ 548.0; Anal. (C, H, N) calcd for $C_{28}H_{45}N_5O_4S$+1.55CF_3COOH: C 50.56, H 6.48, N 9.67; found C 50.95, H 5.92, N 10.27.

Example 23

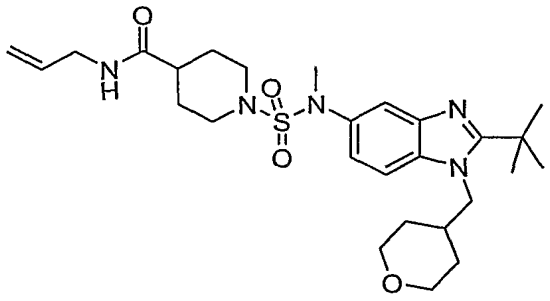
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2,2,2-trifluoroethyl)piperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (100 mg, 0.20 mmol), diisopropylethylamine (0.1 mL, 0.61 mmol), 2,2,2-trifluoroethylamine (0.050 mL, 0.61 mmol), DMF (3 mL), and HATU (116 mg, 0.31 mmol) provided the title compound as its TFA salt (59.2 mg, 42 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 - 1.70 (m, 6 H), 1.72 (s, 9 H), 1.76 - 1.85 (m, 2 H), 2.25 - 2.39 (m, 2 H), 2.72 - 2.84 (m, 2 H), 3.28 - 3.41 (m, 5 H), 3.58 - 3.65 (m, 2 H), 3.82 - 3.94 (m, 2 H), 4.00 - 4.07 (m, 2 H), 4.38 (d, J=7.42 Hz, 2 H), 7.05 - 7.14 (m, 1 H), 7.56 (d, J=8.98 Hz, 1 H), 7.68 (dd, J=8.98, 1.46 Hz, 1 H), 7.91 - 7.94 (m, 1 H); MS (ESI) $(M+H)^+$ 573.8; Anal. (C, H, N) calcd for $C_{26}H_{38}F_3N_5O_4S$+1.85CF_3COOH: C 54.44, H 6.68, N 12.21; found C 45.49, H 4.94, N 8.87.

Example 24

***N*-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide**

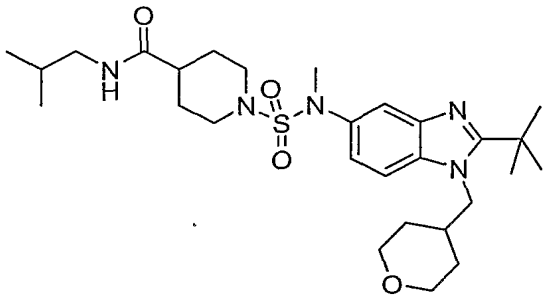


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-

yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (100 mg, 0.20 mmol), diisopropylethylamine (0.1 mL, 0.61 mmol), allylamine (0.1 mL, 0.61 mmol), DMF (3 mL), and HATU (116 mg, 0.31 mmol) provided the title compound as its TFA salt (27.6 mg, 25 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.51 - 1.79 (m, 17 H), 1.80 - 1.90 (m, 2 H), 2.76 - 2.88 (m, 2 H), 3.33 (s, 3 H), 3.34 - 3.41 (m, 2 H), 3.63 - 3.72 (m, 2 H), 3.82 - 3.89 (m, 2 H), 3.98 - 4.08 (m, 2 H), 4.36 (d, J=7.42 Hz, 2 H), 5.07 - 5.20 (m, 2 H), 5.75 - 5.89 (m, 1 H), 6.25 - 6.33 (m, 1 H), 7.52 (d, J=8.98 Hz, 1 H), 7.69 (dd, J=8.98, 1.95 Hz, 1 H), 7.94 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ 532.0;

Example 25

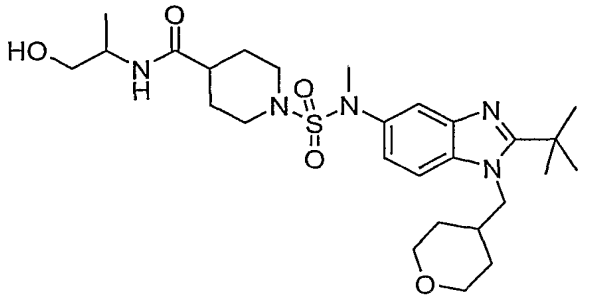
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isobutylpiperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (200 mg, 0.41 mmol), diisopropylethylamine (0.2 mL, 1.22 mmol), isobutylamine (0.12 mL, 1.22 mmol), DMF (6 mL), and HATU (236 mg, 0.62 mmol) provided the title compound as its TFA salt (99.6 mg, 37 %) following purification by reversed-phase HPLC (10-70% CH_3CN in H_2O). ^1H NMR (400 MHz, CD_3OD) δ 0.87 (d, J=6.84 Hz, 6 H) 1.51 - 1.67 (m, 7 H) 1.69 (s, 9 H) 1.70 - 1.77 (m, 3 H) 2.23 - 2.33 (m, 1 H) 2.81 - 2.91 (m, 2 H) 2.91 - 2.99 (m, 2 H) 3.33 (s, 3 H) 3.33 - 3.39 (m, 2 H) 3.66 - 3.74 (m, 2 H) 3.90 - 3.97 (m, 2 H) 4.54 (d, J=7.42 Hz, 2 H) 7.68 (dd, J=8.98, 1.95 Hz, 1 H) 7.81 (d, J=1.95 Hz, 1 H) 7.96 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 458.0.

Example 26

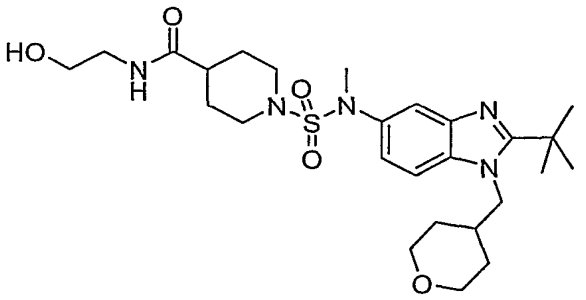
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxy-1-methylethyl)piperidine-4-carboxamide



Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (175 mg, 0.36 mmol), diisopropylethylamine (0.15 mL, 0.85 mmol), DL-2-amino-1-propanol (0.08 mL, 1.07 mmol), DMF (5 mL), and HATU (162 mg, 0.43 mmol) provided the title compound as its TFA salt (66.9 mg, 28 %) following purification by reversed-phase HPLC (10-40% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J=6.64 Hz, 3 H) 1.51 - 1.68 (m, 7 H) 1.72 (s, 9 H) 1.75 - 1.86 (m, 1 H) 2.19 - 2.41 (m, 2 H) 2.67 - 2.91 (m, 2 H) 3.32 (s, 2 H) 3.33 - 3.41 (m, 3 H) 3.43 - 3.70 (m, 4 H) 3.97 - 4.09 (m, 3 H) 4.39 (d, J=7.62 Hz, 2 H) 6.76 (d, J=7.42 Hz, 1 H) 7.55 - 7.60 (m, 1 H) 7.64 - 7.68 (m, 1 H) 7.84 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ 549.8.

Example 27

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperidine-4-carboxamide

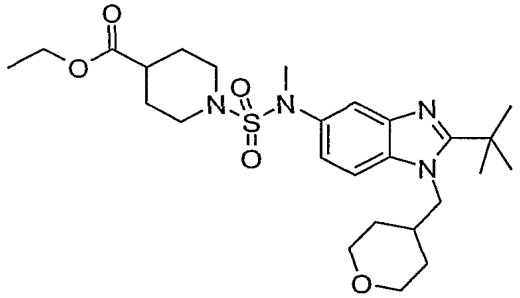


Following the procedure for Step A in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylic acid (70 mg, 0.14 mmol),

diisopropylethylamine (0.042 mL, 0.24 mmol), ethanolamine (0.010 mL, 0.17 mmol), DMF (3 mL), and HATU (59.4 mg, 0.16 mmol) provided the title compound as its TFA salt (46.4 mg, 50 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 - 1.66 (m, 6 H), 1.72 (s, 9 H), 1.82 (d, J=12.50 Hz, 2 H), 2.22 - 2.42 (m, 2 H), 2.71 - 2.83 (m, 2 H), 3.30 (s, 3 H), 3.32 - 3.44 (m, 4 H), 3.52 - 3.65 (m, 2 H), 3.66 - 3.78 (m, 2 H), 3.98 - 4.07 (m, 2 H), 4.39 (d, J=7.42 Hz, 2 H), 7.15 - 7.24 (m, J=32.62 Hz, 1 H), 7.56 - 7.62 (m, 1 H), 7.63 - 7.67 (m, 1 H), 7.81 - 7.88 (m, 1 H); MS (ESI) $(M+H)^+$ 536.0; Anal. (C, H, N) calcd for $C_{26}H_{41}N_5O_5S+2.20CF_3COOH+1.00H_2O$: C 45.38, H 5.66, N 8.70; found C 47.93, H 5.22, N 8.91.

Example 28

Ethyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate

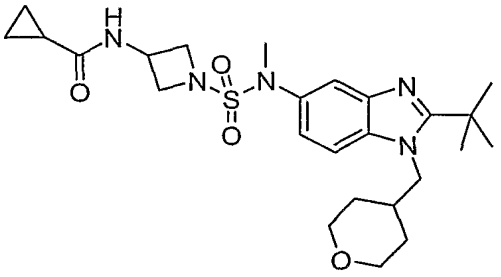


Following the procedure for Step J in Example 10, using 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (1.9 g, 4.25 mmol) and diisopropylethylamine (0.1 mL, 0.6 mmol) at room temperature in MeCN (40 mL) and ethyl isonipecotate (1.9 mL, 12.75 mmol), the solution was concentrated and the residue was redissolved in EtOAc (100 mL). The solution was washed with H_2O (3 x 30 mL), brine (30 mL), dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by flash chromatography (0-100% EtOAc in hexanes, 50min; 100% EtOAc, 10min; 0-2% MeOH in EtOAc, 10min) to provide the title compound (445 mg, 20%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J=7.23 Hz, 3 H), 1.49 - 1.59 (m, 13 H), 1.64 - 1.77 (m, 2 H), 1.86 - 1.95 (m, 2 H), 2.22 - 2.39 (m, 2 H), 2.78 - 2.89 (m, 2 H), 3.28 (s, 3 H), 3.29 - 3.37 (m, 2 H), 3.63 - 3.71 (m, 2 H), 3.95 - 4.02 (m, 2 H), 4.13 (q, J=7.23 Hz, 2 H), 4.20 (d, J=7.42 Hz, 2 H), 7.30 (s, 1 H), 7.32 (d, J=1.95 Hz, 1 H), 7.72 (d, J=1.56 Hz, 1

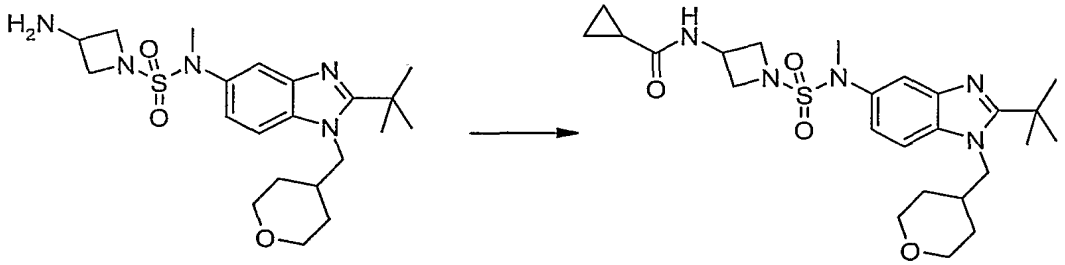
H); MS (ESI) $(M+H)^+$ 521.0; Anal. (C, H, N) calcd for $C_{26}H_{40}N_4O_5S+0.60CH_3OH$: C 59.17, H 7.92, N 10.38; found C 59.23, H 8.03, N 10.45.

Example 29

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclopropanecarboxamide**



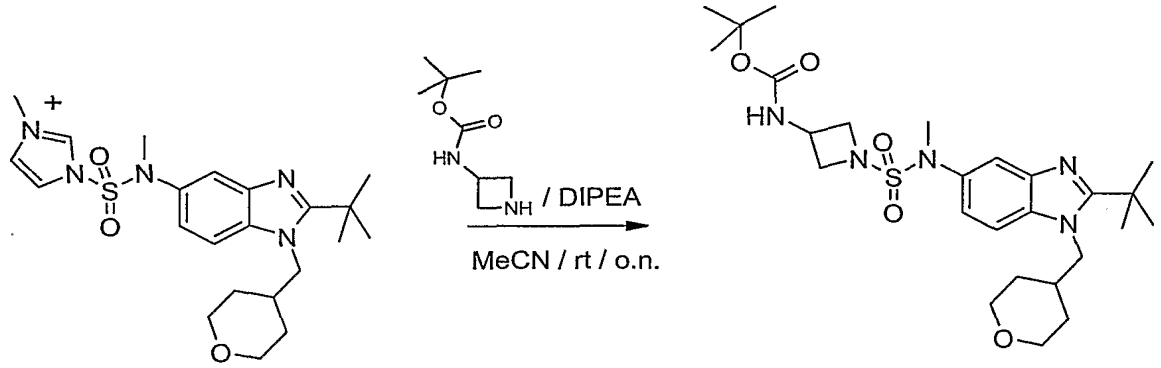
Step A. *N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclopropanecarboxamide



To a solution of 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (150 mg, 0.27 mmol, see Steps B and C for its preparation), diisopropylethylamine (0.14 mL, 0.82 mmol), and cyclopropanecarboxylic acid (0.33 mL, 0.41 mmol) at room temperature in DMF (1.5 mL), was added HATU (125.5 mg, 0.33 mmol) in one portion. The solution was stirred at room temperature for 3 hours. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-65% CH_3CN in H_2O) to provide the title compound as its TFA salt (27.3 mg, 16%). ^1H NMR (400 MHz, CD_3OD) δ 0.72 - 0.85 (m, 4 H) 1.50 - 1.68 (m, 5 H) 1.69 (s, 9 H) 2.31 - 2.46 (m, 1 H) 3.31 - 3.40 (m, 5 H) 3.80 - 3.86 (m, 2 H) 3.91 - 3.98 (m, 2 H) 4.00 - 4.06 (m, 2 H) 4.50 - 4.59 (m, 3 H)

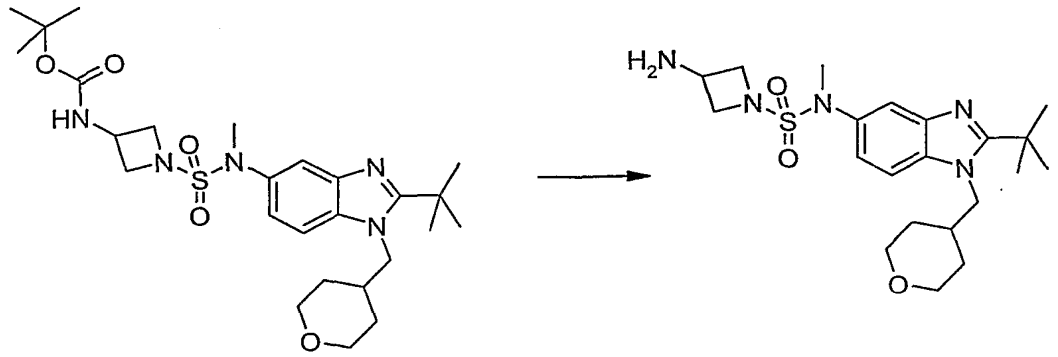
7.67 (dd, J=8.98, 2.15 Hz, 1 H) 7.79 (d, J=2.15 Hz, 1 H) 7.96 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 503.8; Anal. (C, H, N) calcd for $C_{25}H_{39}N_5O_4S+1.80CF_3COOH+0.05H_2O$ $+0.45CH_3OH$: C 48.18, H 5.66, N 9.67; found C 48.19, H 5.67, N 9.69.

Step B. 3-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (2.2 g, 4.9 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (2.6 mL, 14.7 mmol) at rt in MeCN (30 mL), was added 3-*N*-Boc-amino-azetidine (1.0 g, 5.9 mmol). The solution was stirred at rt overnight. After evaporation of the solvent, the residue was purified by flash chromatography (0-100% EtOAc in hexanes, 50 min; 100% EtOAc 10 min; 0-2% MeOH in EtOAc, 10 min) to provide the title compound (0.95 g, 36%). ^{1}H NMR (400 MHz, CD_3OD) δ 1.40 (s, 9 H) 1.49 - 1.65 (m, 5 H) 1.68 (s, 9 H) 2.30 - 2.45 (m, 1 H) 3.32 (s, 3 H) 3.33 - 3.39 (m, 2 H) 3.75 - 3.81 (m, 2 H) 3.89 - 4.00 (m, 4 H) 4.53 (d, J=7.62 Hz, 2 H) 7.65 (dd, J=8.98, 2.15 Hz, 1 H) 7.78 (d, J=2.15 Hz, 1 H) 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 535.8; Anal. (C, H, N) calcd for $C_{26}H_{41}N_5O_5S+2.10CF_3COOH+0.60H_2O+0.45CH_3CN$: C 46.44, H 5.72, N 9.49; found C 46.42, H 5.73, N 9.51.

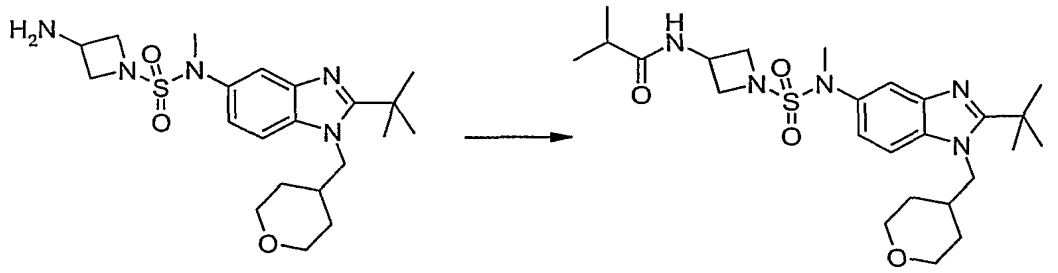
Step C. 3-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide



To a solution of *tert*-butyl (1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)carbamate (0.95 g, 1.77 mmol, see Step B for its preparation) at 0°C in DCM (6 mL), was added TFA (6 mL, excess) dropwise. The solution was stirred at 0°C for 20 min. The solution was concentrated. The residue was redissolved in DCM, washed with 1N NaOH (x2), the aqueous layers were extracted with DCM (x4), the combined organic layers were dried over Na_2SO_4, and subjected to filtration. Evaporation of the solvent provided the title compound (778 mg, 100%). MS (ESI) $(M+H)^+$ 436.1.

Example 30

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)-2-methylpropanamide**

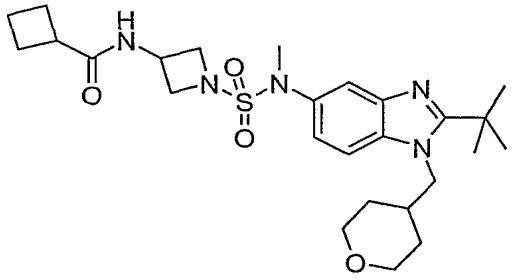


To a solution of 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (150 mg, 0.27 mmol, see Example 29, Steps B and C for its preparation) and diisopropylethylamine (0.1 mL, 0.57 mmol) in DCM (3 mL) at 0°C, was added isobutyryl chloride (0.06 mL, 0.57 mmol) dropwise. The solution was stirred at room temperature for 1.5 hours. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-60% CH_3CN in H_2O) to provide the title compound as its TFA salt (21.7 mg, 15%). ^1H NMR (400 MHz, CD_3OD) δ 1.07 (d, J=7.03 Hz, 6 H) 1.49 - 1.67 (m, 5 H) 1.68 (s, 9

H) 2.32 - 2.46 (m, 2 H) 3.30 - 3.39 (m, 5 H) 3.78 - 3.84 (m, 2 H) 3.90 - 3.97 (m, 2 H) 3.99 - 4.05 (m, 2 H) 4.53 (d, J=7.42 Hz, 2 H) 7.65 (dd, J=8.98, 1.95 Hz, 1 H) 7.78 (d, J=1.95 Hz, 1 H) 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 505.8; Anal. (C, H, N) calcd for $C_{25}H_{39}N_5O_4S+1.60CF_3COOH+0.35CH_3CN$: C 49.41, H 5.98, N 10.67; found C 49.55, H 5.84, N 10.61.

Example 31

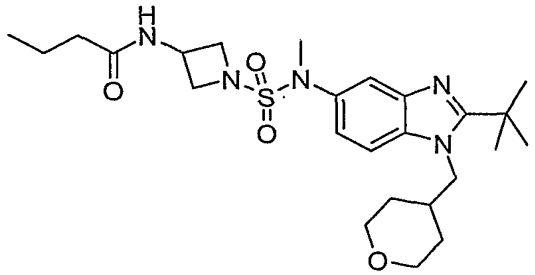
***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclobutanecarboxamide**



Following the procedure for Step A in Example 30, using 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (100 mg, 0.23 mmol), diisopropylethylamine (0.1 mL, 0.57 mmol), DCM (3 mL), and cyclobutane carbonyl chloride (0.07 mL, 0.57 mmol) provided the title compound as its TFA salt (11.8 mg, 8 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, CD_3OD) δ 1.26 - 1.32 (m, 1 H) 1.49 - 1.66 (m, 5 H) 1.68 (s, 9 H) 1.78 - 1.88 (m, 1 H) 1.92 - 2.01 (m, 1 H) 2.04 - 2.24 (m, 4 H) 3.32 (s, 3 H) 3.33 - 3.40 (m, 2 H) 3.78 - 3.84 (m, 2 H) 3.90 - 3.98 (m, 2 H) 3.99 - 4.05 (m, 2 H) 4.47 - 4.56 (m 3 H) 7.64 (dd, J=9.08, 2.05 Hz, 1 H) 7.77 (d, J=2.05 Hz, 1 H) 7.94 (d, J=9.08 Hz, 1 H); MS (ESI) $(M+H)^+$ 517.8.

Example 32

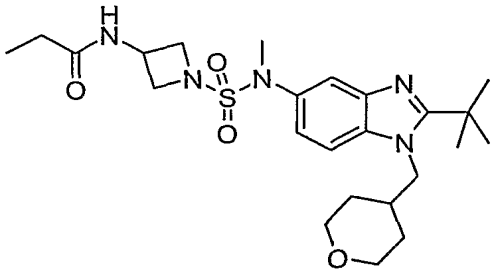
***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)butanamide**



Following the procedure for Step A in Example 30, using 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (100 mg, 0.23 mmol), diisopropylethylamine (0.1 mL, 0.57 mmol), DCM (3 mL), and butyryl chloride (0.06 mL, 0.57 mmol) provided the title compound as its TFA salt (11.8 mg, 8 %) following purification by reversed-phase HPLC (10-60% CH_3CN in H_2O). ^1H NMR (400 MHz, CD_3OD) δ 0.90 (t, J=7.42 Hz, 3 H) 1.50 - 1.66 (m, 7 H) 1.68 (s, 9 H) 2.14 (t, J=7.42 Hz, 2 H) 2.31 - 2.44 (m, 1 H) 3.32 (s, 3 H) 3.33 - 3.39 (m, 2 H) 3.78 - 3.84 (m, 2 H) 3.90 - 3.97 (m, 2 H) 4.00 - 4.05 (m, 2 H) 4.53 (d, J=7.62 Hz, 2 H) 7.65 (dd, J=8.98, 1.95 Hz, 1 H) 7.78 (d, J=1.95 Hz, 1 H) 7.95 (d, J=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 505.8; Anal. (C, H, N) calcd for $C_{25}H_{39}N_5O_4S+1.75CF_3COOH+0.20H_2O+0.10CH_3CN$: C 48.35, H 5.86, N 10.02; found C 48.33, H 5.86, N 10.01.

Example 33

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)propanamide**

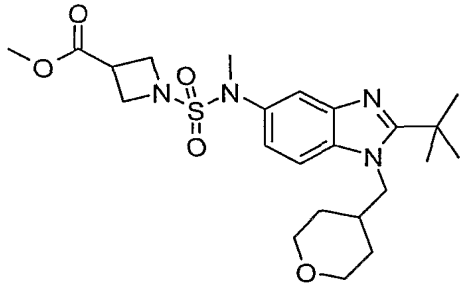


Following the procedure for Step A in Example 29, using 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (150 mg, 0.27 mmol), diisopropylethylamine (0.14 mL, 0.82 mmol), DMF (1.5 mL), propionic acid (0.031 mL, 0.41 mmol) and HATU (125.5 mg, 0.33 mmol) provided the title compound as its TFA salt (15.5 mg, 9.5 %) following

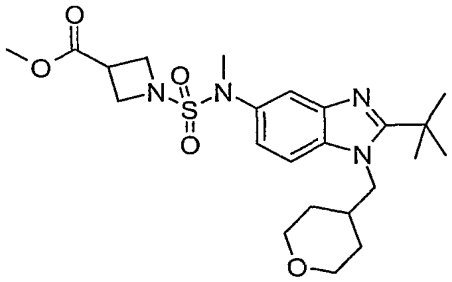
purification by reversed-phase HPLC (10-40% CH_3CN in H_2O). ^1H NMR (400 MHz, CD_3OD) δ 1.13 (t, J=7.62 Hz, 3 H) 1.51 - 1.72 (m, 5 H) 1.74 (s, 9 H) 2.28 (q, J=7.62 Hz, 2 H) 3.31 (s, 3 H) 3.32 - 3.40 (m, 2 H) 3.71 - 3.77 (m, 2 H) 4.00 - 4.07 (m, 2 H) 4.30 - 4.40 (m, 4 H) 4.64 - 4.75 (m, 1 H) 7.50 - 7.54 (m, 1 H) 7.57 - 7.61 (m, 1 H) 8.26 - 8.31 (m, 1 H) 8.34 (d, J=1.37 Hz, 1 H); MS (ESI) $(M+H)^+$ 491.8.

Example 34

Methyl 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidine-3-carboxylate



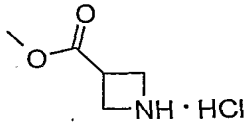
Step A. Methyl 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidine-3-carboxylate



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.17 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.12 mL, 0.68 mmol) at rt in MeCN (0.8 mL), was added methyl azetidine-3-carboxylate hydrochloride (51.5 mg, 0.34 mmol). The solution was stirred at rt overnight. After evaporation of the solvent, the residue was purified by flash chromatography (0-100% EtOAc in hexanes, 50 min; 100% EtOAc 10 min; 0-2% MeOH in EtOAc, 10 min) to provide the title compound (7.8 mg, 8%). ^1H NMR (400 MHz, CD_3OD) δ 1.50 - 1.55 (m, 5 H) 1.56 (s, 9 H) 2.23 - 2.36 (m, 1 H) 3.29 (s, 3 H)

3.30 - 3.42 (m, 2 H) 3.75 (s, 3 H) 3.95 - 4.08 (m, 4 H) 4.10 - 4.23 (m, 4 H) 7.28 - 7.31 (m, 2 H) 7.71 - 7.74 (m, 1 H); MS (ESI) $(M+H)^+$ 478.8.

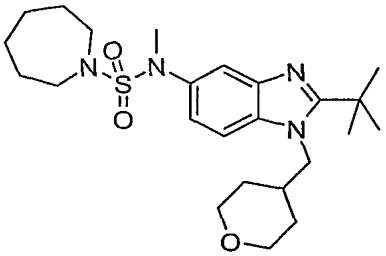
Step B. Methyl azetidine-3-carboxylate hydrochloride



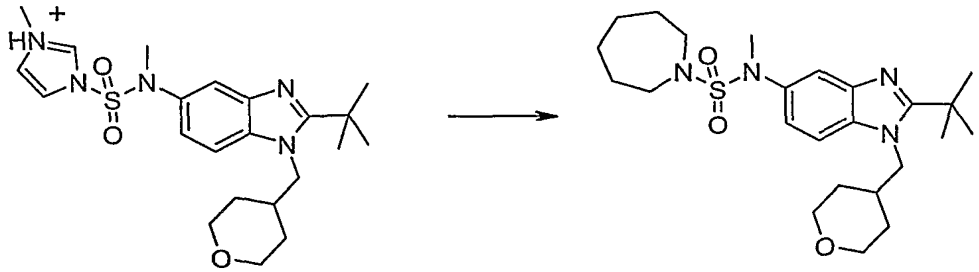
To a stirring suspension of 3-azetidine carboxylic acid in MeOH at 0°C, was added $SOCl_2$ dropwise. After 20 minutes, the ice bath was removed, the solution was warmed to rt and was stirred for 2 hours. The solvent was removed *in vaccuo* to afford the title compound as its HCl salt (1.5g, 100%). ^1H NMR (400 MHz, CD_3OD) δ 3.71 - 3.77 (m, 1 H) 3.77 (s, 3 H) 4.18 - 4.31 (m, 4 H).

Example 35

***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]hexahydro-*N*-methyl-1*H*-azepine-1-sulfonamide**



Step A. *N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]hexahydro-*N*-methyl-1*H*-azepine-1-sulfonamide

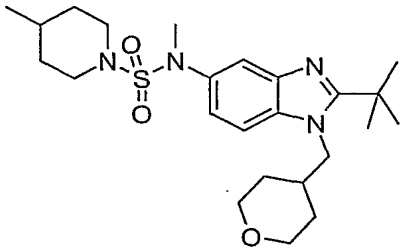


To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine

(0.045 mL, 0.26 mmol) at rt in DMF (1.2 mL), was added hexamethyleneimine (0.025 mL, 0.22 mmol). The solution was stirred at 80°C for 1 hour. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (20-50% MeCN in H_20) to provide the title compound as its TFA salt (23 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.61 (m, 8 H), 1.71 (m, 13 H), 2.27-2.35 (m, 1 H), 3.26 (s, 3 H), 3.30-3.37 (m, 6 H), 4.01-4.03 (m, 2 H), 4.34 (d, J=7.42 Hz, 2 H), 7.48 (d, J=8.96 Hz, 1 H), 7.68 (dd, J=8.96, 1.79 Hz, 1 H), 7.88 (d, J=1.79 Hz, 1 H); MS (ESI) $(M+H)^+$ 463.0; Anal. (C, H, N) calcd for $C_{24}H_{38}N_4O_3S$+1.30CF_3COOH+1.10H_2O: C 50.66, H 6.63, N 8.88;. found C 50.64, H 6.59, N 8.92.

Example 36

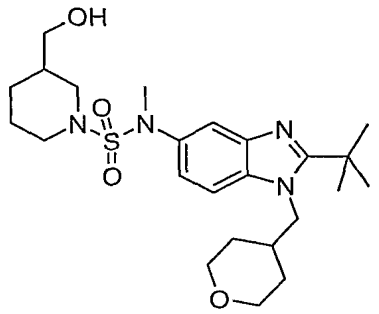
***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-*N*,4-dimethyl-1-piperidinesulfonamide**



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.045 mL, 0.26 mmol) at rt in DMF (1.0 mL), was added 4-methylpiperidine (0.026 mL, 0.22 mmol). The solution was stirred at 80°C for 1.5 hours. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (20-50% MeCN in H_2O) to provide the title compound as its TFA salt (27.3 mg, 22%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (d, J=6.67 Hz, 3 H), 1.17-1.25 (m, 2 H), 1.46-1.66(m, 7 H), 1.71 (s, 9 H), 2.27-2.35 (m, 1 H), 2.79-2.83 (m, 2 H), 3.29 (s, 3 H), 3.33-3.37 (m, 2 H), 3.65-3.67 (m, 2 H), 4.02-4.03 (m, 2 H), 4.34-4.35 (d, 2 H), 7.49 (d, J=8.96 Hz, 1 H), 7.67 (d, J=8.96 Hz, 1 H), 7.91 (s, 1 H); MS (ESI) $(M+H)^+$ 463.0; Anal. (C, H, N) calcd for $C_{24}H_{38}N_4O_3S$+1.40CF_3COOH+0.30H_2O: C 51.28, H 6.42, N 8.93; found C 51.36, H 6.34, N 8.79.

Example 37

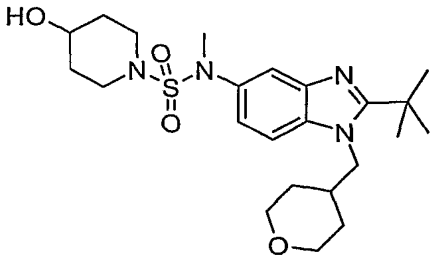
***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-(hydroxymethyl)-*N*-methyl-1-piperidinesulfonamide**



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.045 mL, 0.26 mmol) at rt in DMF (1.0 mL), was added 3-piperidine methanol (25.3 mg, 0.22 mmol). The solution was stirred at 80°C for 1.5 hours. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-90% MeCN in H_20) to provide the title compound as its TFA salt (24.3 mg, 19%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04-1.10 (m, 1 H), 1.52-1.61 (m, 5 H), 1.71 (m, 12 H), 1.79-1.87 (m, 1 H), 2.28-2.35 (m, 1 H), 2.59-2.62 (m, 1 H), 2.87-2.90 (m, 1 H), 3.31 (s, 3 H), 3.32-3.38 (m, 3 H), 3.60-3.65 (m, 3 H), 4.02-4.04 (m, 2 H), 4.36 (d, J=7.42 Hz, 2 H), 7.50 (d, J=8.70 Hz, 1 H), 7.67 (d, J=8.70 Hz, 1 H), 8.07 (s, 1 H); MS (ESI) $(M+H)^+$ 479.0; Anal. (C, H, N) calcd for $C_{24}H_{38}N_4O_4S$+1.30CF_3COOH+0.90H_2O +0.20CH_3OH: C 49.56, H 6.50, N 8.63; found C 49.53, H 6.48, N 8.58.

Example 38

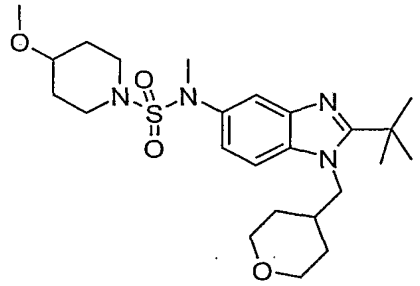
***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-hydroxy-*N*-methyl-1-piperidinesulfonamide**



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.045 mL, 0.26 mmol) at rt in DMF (1.0 mL), was added 4-hydroxypiperidine (22.3 mg, 0.22 mmol). The solution was stirred at 80°C for 1.5 hours. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-95% MeCN in H_2O) to provide the title compound as its TFA salt (18.9 mg, 15%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.54-1.65 (m, 6 H), 1.72 (s, 9 H), 1.86-1.90 (m, 2 H), 2.28-2.36 (m, 1 H), 3.07-3.11 (m, 2 H), 3.33 (s, 3 H), 3.33-3.38 (m, 2 H), 3.48-3.52 (m, 2 H), 3.79-3.82 (m, 1 H), 4.02-4.04 (m, 2 H), 4.36 (d, J=7.42 Hz, 2 H), 7.51 (d, J=8.96 Hz, 1 H), 7.68 (dd, J=8.96, 1.66 Hz, 1 H), 8.07 (d, J=1.66 Hz, 1 H); MS (ESI) $(M+H)^+$ 465.0; Anal. (C, H, N) calcd for $C_{23}H_{36}N_4O_4S$+1.10CF_3COOH+0.30H_2O +0.40CH_3OH: C 50.55, H 6.51, N 9.21; found C 50.53, H 6.50, N 9.19.

Example 39

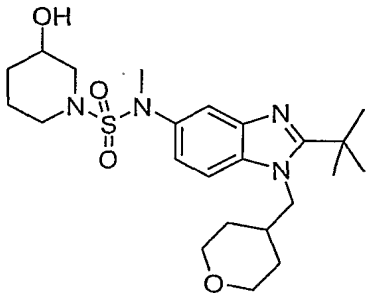
***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-methoxy-*N*-methyl-1-piperidinesulfonamide**



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.090 mL, 0.53 mmol) at rt in DMF (1.0 mL), was added 4-methoxypiperidine hydrochloride (25.3 mg, 0.22 mmol). The solution was stirred at 80°C for 1 hour. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (20-50% MeCN in H_20) to provide the title compound as its TFA salt (6.74 mg, 5%). MS (ESI) $(M+H)^+$ 479.0.

Example 40

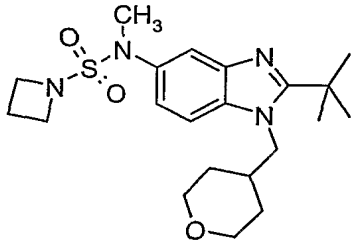
***N*-[2-(1,1-Dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-hydroxy-*N*-methyl-1-piperidinesulfonamide**



To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium (100 mg, 0.22 mmol, see Example 10, Steps B-I for its preparation) and diisopropylethylamine (0.090 mL, 0.53 mmol) at rt in DMF (1.0 mL), was added 3-hydroxypiperidine (22.3 mg, 0.22 mmol). The solution was stirred at 80°C for 1 hour. After evaporation of the solvent, the residue was purified by reversed-phase HPLC (10-90% MeCN in H_20) to provide the title compound as its TFA salt (16.0 mg, 13%). MS (ESI) $(M+H)^+$ 465.0.

Example 41

N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide

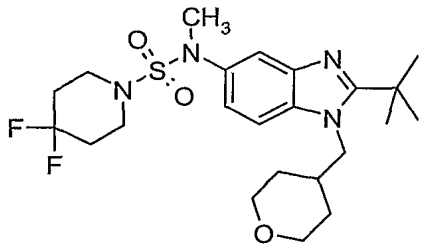


To a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate in acetonitrile (2.8 mL, 0.344 mmol) (for preparation, see Example 2, Step G) was added azetidine (35 μL; 0.516 mmol). The reaction mixture was stirred at room temperature overnight, then Hunig's base (72 μL; 0.413 mmol) was added and the reaction mixture stirred at room temperature for another day. The reaction mixture was

concentrated under reduced pressure. The residue was taken in ethyl acetate and washed with 1N hydrochloric acid, 2N sodium hydroxide, brine and water. The aqueous layers were combined and extracted with ethyl acetate. Organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography provided the title compound (14.5 mg, 10 %). ^{1}H NMR (600 MHz, CD_3OD) δ 1.40-1.53 (m, 4H), 1.57 (s, 9H), 2.14 (q, J = 7.68Hz, 2H), 2.23-2.33 (m, 1H), 3.22 (s, 3H), 3.25 (m, 2H), 3.80 (t, J = 7.68Hz, 4H), 3.84 (dd, J = 11.26, 3.58Hz, 2H), 4.41 (d, J = 7.42Hz, 2H), 7.51 (d, J = 8.70Hz, 1H), 7.67 (d, J = 1.79Hz, 1H), 7.80 (d, J = 8.45Hz, 1H); MS (ESI) $(M+H)^+$ 421.0

Example 42

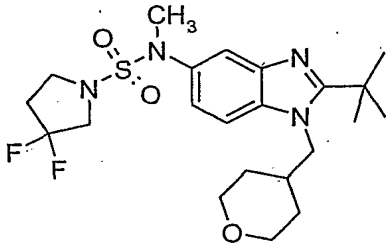
N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4,4-difluoro-N-methylpiperidine-1-sulfonamide



Following the procedure for Step A in Example 41, using 4,4-difluoropiperidine (63 mg; 0.516 mmol) and Hunig's base (72 μL; 0.413 mmol) provided the title compound (68.4 mg; 41%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.42-1.57 (m, 4H), 1.60 (s, 9H), 1.90 (m, 4H), 2.26-2.34 (br s, 1H), 3.24 (s, 3H), 3.25-3.34 (m, 6H), 3.84 (dd, J = 10.75, 2.56Hz, 2H), 4.46 (d, J = 6.91Hz, 2H), 7.60 (d, J = 8.19Hz, 1H), 7.76 (s, 1H), 7.90 (d, J = 8.70Hz, 1H); MS (ESI) $(M+H)^+$ 485.0

Example 43

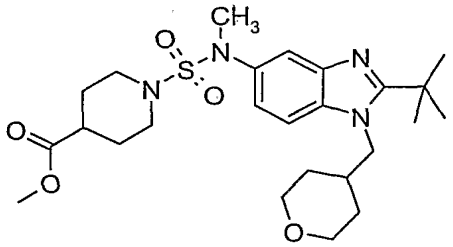
N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-3,3-difluoro-N-methylpyrrolidine-1-sulfonamide



Following the procedure for Step A in Example 41, using 3,3-difluoropyrrolidine (55 mg; 0.516 mmol) and Hunig's base (72 μL; 0.413 mmol) provided the title compound (40.0 mg; 24%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.40-1.55 (m, 4H), 1.59 (s, 9H), 2.22-2.37 (m, 3H), 3.21-3.31 (m, 2H), 3.25 (s, 3H), 3.44 (t, J = 7.17Hz, 2H), 3.52 (t, J = 12.80Hz, 2H), 3.84 (m, 2H), 4.45 (d, J = 7.17Hz, 2H), 7.59 (d, J = 7.94Hz, 1H), 7.74 (s, 1H), 7.89 (d, J = 8.70Hz, 1H); MS (ESI) (M+H)+ 471.0

Example 44

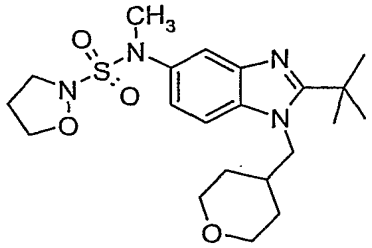
Methyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate



Following the procedure for Step A in Example 41, using methyl isonipecotate (70 μL; 0.516 mmol) and Hunig's base (72 μL; 0.413 mmol) provided the title compound (71.5 mg; 41%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.37-1.55 (m, 6H), 1.59 (s, 9H), 1.78 (m, 2H), 2.24-2.33 (br. s, 1H), 2.38 (m, 1H), 2.82 (m, 2H), 3.17-3.30 (m, 2H), 3.22 (s, 3H), 3.47-3.61 (m, 2H), 3.54 (s, 3H), 3.83 (d, J = 8.45Hz, 2H), 4.45 (d, J = 7.17Hz, 2H), 7.57 (d, J = 7.94Hz, 1H), 7.75 (s, 1H), 7.87 (d, J = 8.45Hz, 1H); MS (ESI) (M+H)+ 507.0

Example 45

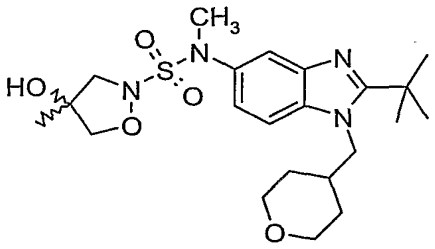
N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide



Following the procedure for Step A in Example 41, using isoxazolidine (57 mg; 0.516 mmol) and Hunig's base (132 μL; 0.757 mmol) provided the title compound (51.3 mg; 34%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.43-1.56 (m, 4H), 1.60 (s, 9H), 2.22-2.35 (m, 3H), 3.26 (m, 2H), 3.37 (s, 3H), 3.47 (t, J = 7.17Hz, 2H), 3.85 (m, 2H), 4.03 (t, J = 7.30Hz, 2H), 4.46 (d, J = 7.17Hz, 2H), 7.63 (dd, J = 8.70, 1.02Hz, 1H), 7.80-7.84 (d, J = 1.28Hz, 1H), 7.88 (d, J = 8.96Hz, 1H); MS (ESI) (M+H)+ 437.0

Example 46

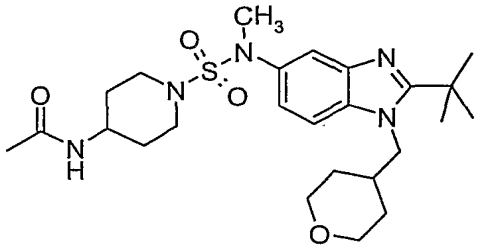
(4R)-N-[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-hydroxy-N,4-dimethylisoxazolidine-2-sulfonamide



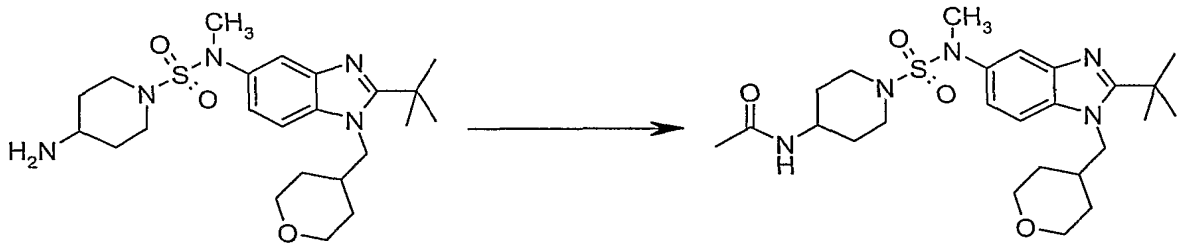
Following the procedure for Step A in Example 41, using 4-methylisoxazolidin-4-ol (57 mg; 0.41 mmol) and Hunig's base (57 μL; 0.33 mmol) provided the title compound. ^{1}H NMR (600 MHz, CD_3OD) δ 1.35 (s, 3H), 1.41-1.55 (m, 4H), 1.57 (s, 9H), 2.22-2.33 (m, 1H), 3.19 (s, 3H), 3.24 (m, 2H), 3.30-3.36 (m, 2H), 3.46 (d, J = 11.52Hz, 1H), 3.77-3.90 (m, 4H), 4.43 (d, J = 7.42Hz, 2H), 7.61 (d, J = 8.96Hz, 1H), 7.79 (s, 1H), 7.85 (d, J = 8.96Hz, 1H); MS (ESI) (M+H)+ 467.0

Example 47

N-(1-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide



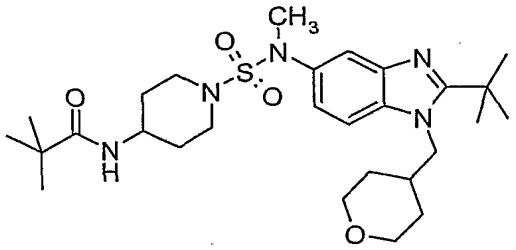
Step B. N-(1-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide



To a solution of 4-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperidine-1-sulfonamide in dichloromethane (0.516 mmol) (the preparation of it has followed the same procedure as for the synthesis of a compound in Example 1, Step J, by using 4-tetrahydropyranmethylamine as the coupling reagent for the SNAr reaction) was added triethylamine (143 μL; 1.032 mmol) followed by acethyl chloride (44 μL; 0.619 mmol). The reaction mixture was stirred at room temperature for two hours then was washed with water. The aqueous layer was extracted with dichloromethane. Combined dichloromethane extracts were dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography provided the title compound (143.8 mg, 55%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.29-1.40 (m, 2H), 1.40-1.54 (m, 4H), 1.58 (s, 9H), 1.74 (m, 2H), 1.81 (s, 3H), 2.27 (br s, 1H), 2.83 (m, 2H), 3.21 (s, 3H), 3.24 (m, 2H), 3.57 (m, 2H), 3.62 (t, J = 10.88Hz, 1H), 3.83 (dd, J = 11.52, 2.56Hz, 2H), 4.44 (d, J = 7.42Hz, 2H), 7.58 (d, J = 8.70Hz, 1H), 7.72 (s, 1H), 7.87 (d, J = 8.96Hz, 1H); MS (ESI) (M+H)+ 506.0

Example 48

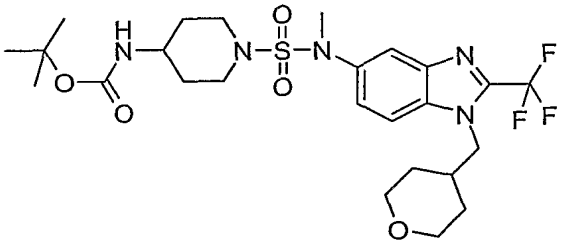
N-(1-{[[2-tert-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide



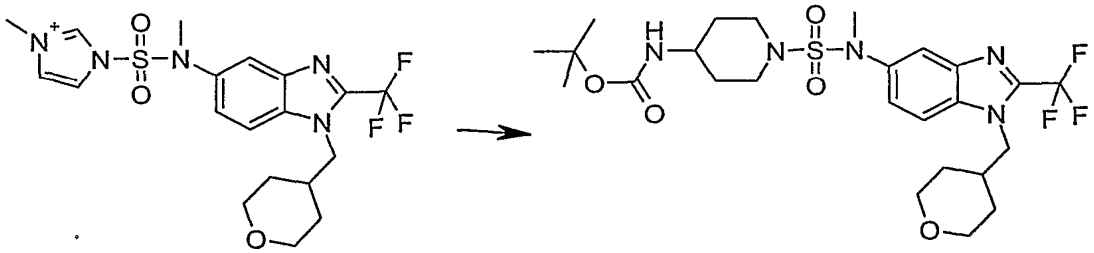
Following the procedure for Step B in Example 47, using trimethyl acetyl chloride (76 μL; 0.619 mmol) and triethylamine (143 μL; 1.032 mmol) provided the title compound (138.1 mg; 49%). ^{1}H NMR (600 MHz, CD_3OD) δ 1.04 (s, 9H), 1.37-1.53 (m, 6H), 1.55 (s, 9H), 1.68 (m, 2H), 2.21-2.32 (m, 1H), 2.77 (m, 2H), 3.20 (s, 3H), 3.24 (m, 2H), 3.57-3.67 (m, 3H), 3.83 (m, 2H), 4.38 (d, J = 7.42Hz, 2H), 7.48 (dd, J = 8.83, 1.41Hz, 1H), 7.68 (d, J = 1.54Hz, 1H), 7.75 (d, J = 8.96Hz, 1H); MS (ESI) (M+H)+ 548.0.

Example 49

***tert*-Butyl [1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]carbamate**



Step A. *tert*-Butyl [1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]carbamate



Following the procedure in Step I of Example 1, 3-methyl-1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)-1*H*-imidazol-3-ium (crude product, 1.0 mmol) (see following steps B, C, D, E, F, G

and H for preparation) was reacted with *tert*-butyl piperidin-4-ylcarbamate (0.40 g, 2.0 mmol). The crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 0.33 g (55%) of a white solid as the title compound. ^{1}HNMR (400 MHz, CHLOROFORM-D): δ 1.41 (s, 9 H), 1.44 - 1.54 (m, 4 H), 1.77 - 1.93 (m, 3 H), 2.20 - 2.33 (m, 1 H), 2.83 - 2.97 (m, 3 H), 3.29 (s, 3 H), 3.32 - 3.44 (m, 3 H), 3.57 - 3.69 (m, 3 H), 3.88 - 3.97 (m, 2 H), 4.33 (d, J=7.42 Hz, 2 H), 7.58 (dd, J=8.79, 1.95 Hz, 1 H), 7.78 (d, J=8.79 Hz, 1 H), 7.85 (d, J=2.15 Hz, 1 H). MS (ESI) $(M+H)^+$ = 576.0. Anal. Calcd for $C_{25}H_{36}F_3N_5O_5S$+ 0.10 TFA+0.10 H_2O+0.40 CH_3OH(624.10): C, 51.58; H, 6.38; N, 11.22; Found: C, 51.56; H, 6.31; N, 11.27.

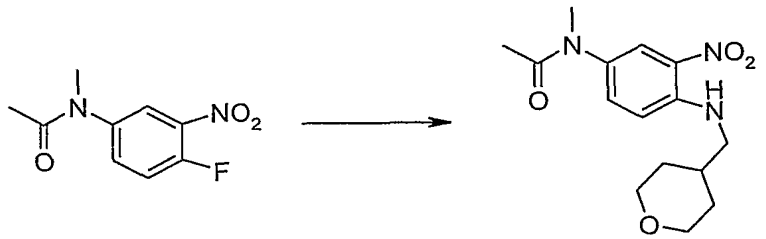
Step B. *N*-(4-Fluoro-3-nitrophenyl)acetamide

4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added in portions to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, *J*=6.44, 2.73 Hz, 1 H).

Step C. *N*-(4-Fluoro-3-nitrophenyl)-*N*-methylacetamide

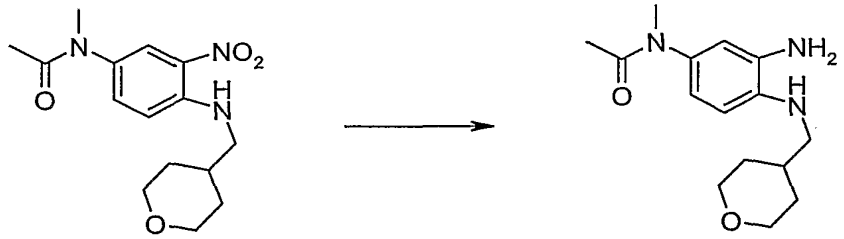
Sodium hydride (4.22 g, 60%, 106 mmol) was added portionwise to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide(13.9 g, 70 mmol) (for preparation, see the step B in Example 1) in THF (200 mL) at 0 °C. Stirring for 20 min, iodomethane (18.5 g, 130 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturaed $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x50 mL). After filtration and concentration, 13.1 g (88%) of the title compound was obtained as a yellow solid. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

Step D. *N*-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



4-Aminomethyltetrahydropyran (10.0 g, 86.5 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (15.6 g, 73.3 mmol) and TEA (15.3 mL, 11.1 g, 110 mmol) in EtOH (300 mL) at room temperature. The reaction mixture was heated for 6 h at reflux. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H_2O (3x50 mL), saturated NaCl (3x50 mL), and dried over Na_2SO_4. After filtation and concentration, 21.7 g (96%) of the title compound was obtained as an orange-red solid. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 - 3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H). MS (ESI) $(M+H)^+ = 309.12$.

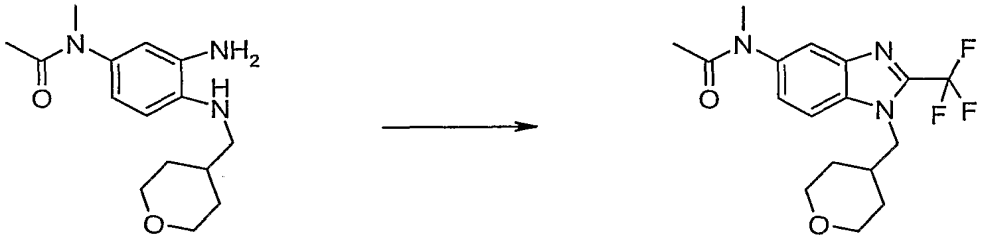
Step E. *N*-{3-Amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide



N-Methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (21.7 g, 70.5 mmol) was hydrogenated in ethyl acetate (500 mL) catalyzed by 10% Pd/C (1.0 g) at 30-40 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 19.6 g (100%) of a purple solid was obtained. ^{1}H NMR (400 MHz, CHLOROFORM-D): δ 1.35 - 1.50 (m, 2 H), 1.67 (s, 1

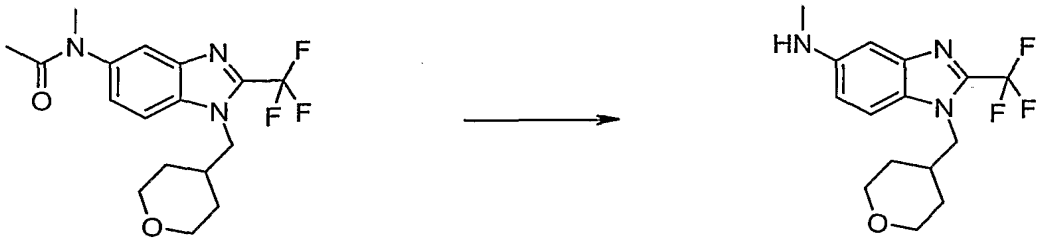
H), 1.73 - 1.81 (m, 2 H), 1.88 (s, 3 H), 1.88 - 1.99 (m, 1 H), 3.04 (d, *J*=6.64 Hz, 2 H), 3.20 (s, 3 H), 3.33 - 3.48 (m, 4 H), 3.97 - 4.08 (m, 2 H), 6.54 (d, *J*=1.76 Hz, 1 H), 6.60 - 6.63 (m, 2 H); MS (ESI) $(M+H)^+ = 278.7$

Step F. *N*-Methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide



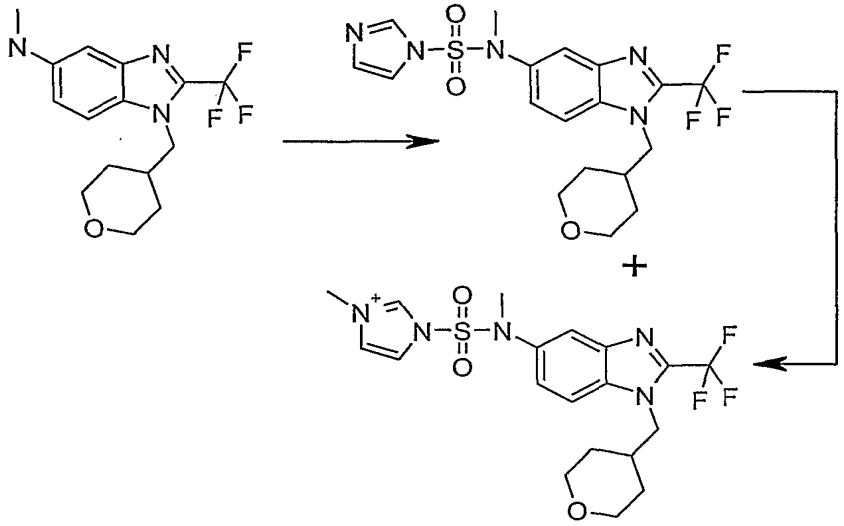
A solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide hydrochoride (2.77 g, 10 mmol) in trifluoroacetic acid (60 mL) was heated to reflux for 18 h. After evaporation of the solvent, the residue was disolved in EtOAc (200 mL), washed with 2*N* NaOH (2x10 mL) and dried over Na_2SO_4. The crude product was purified by MPLC using EtOAc on silica gel to give 3.18 g (90%) of a white solid as the title compound. MS (ESI) $(M+H)^+ = 356.02$.

Step G. *N*-Methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine



N-Methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]acetamide (3.18 g, 8.95 mmol) was dissolved in hydrochloric acid (37%, 60 mL) and then heated overnight at 95°C. After concentration, the residue was treated with 20 mL of 2*N* NaOH, extracted with EtOAc (4x50 mL). The combined organic phaese were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation, 2.80 g (100%) of a purple white solid was obtained as the title product, which was used directly for Step H. MS (ESI) $(M+H)^+ = 314.20$.

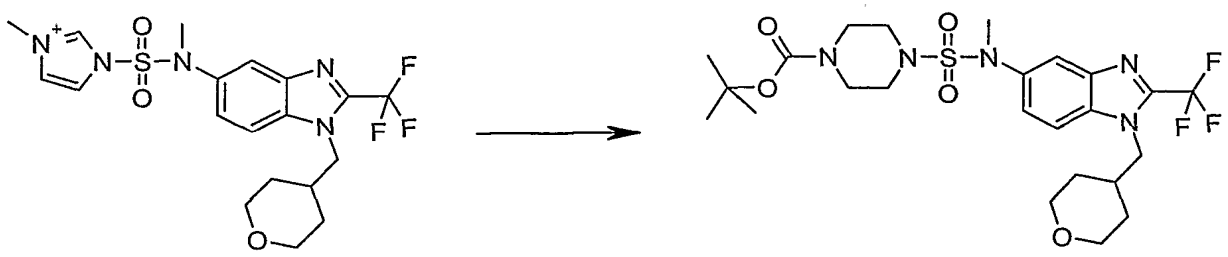
Step H. 3-Methyl-1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)-1*H*-imidazol-3-ium.



Following the procedure in Step H of Example 1, *N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-amine (0.32 g, 1.0 mmol) was converted to 3-methyl-1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)-1*H*-imidazol-3-ium, which was used in Step A without any purification.

Example 50

***tert*-Butyl 4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxylate**

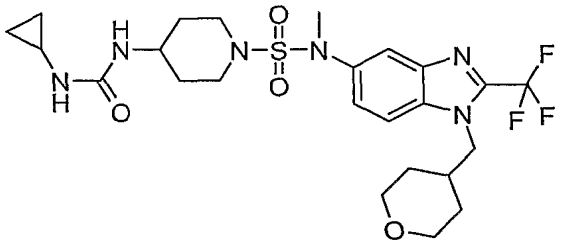


Following the procedure in Step I of Example 1, 3-methyl-1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)-1*H*-imidazol-3-ium (crude product, 1.10 mmol) (for preparation see the step H in

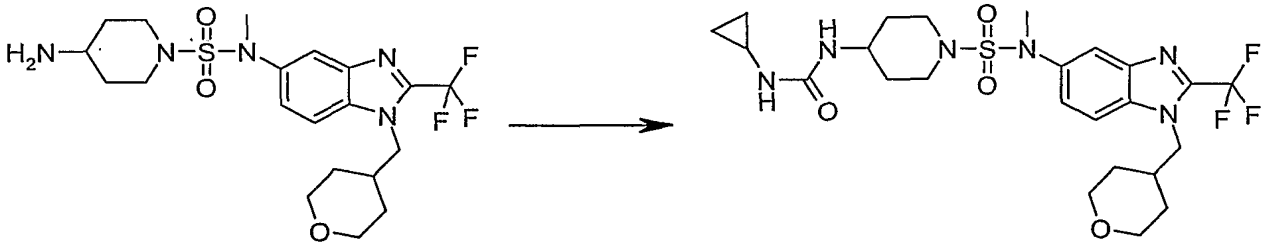
example 4) was reacted with *tert*-butyl piperazine-1-carboxylate (0.38 g, 2.0 mmol). The crude product was purified by MPLC using Hex/EtOAc (1:1) on silica gel to give 0.28 g (45%) of a white solid as the title compound. ^{1}HNMR (400 MHz, CHLOROFORM-D): δ 1.43 (s, 9 H), 1.45 - 1.54 (m, 4 H), 2.19 - 2.33 (m, 1 H), 3.15 - 3.22 (m, 4 H), 3.32 (s, 3 H), 3.33 - 3.37 (m, 2 H), 3.38 - 3.45 (m, 4 H), 3.87 - 3.97 (m, 2 H), 4.33 (d, J=7.62 Hz, 2 H), 7.60 (dd, J=8.89, 2.05 Hz, 1 H), 7.79 (d, J=8.59 Hz, 1 H), 7.87 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ = 562.0; Anal. Calcd for C24H34F3N5O5S+0.70 EtOAc(623.30): C, 51.64; H, 6.40; N, 11.24; Found: C, 51.60; H, 5.80; N, 11.13.

Example 51

4-{[(Cyclopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide



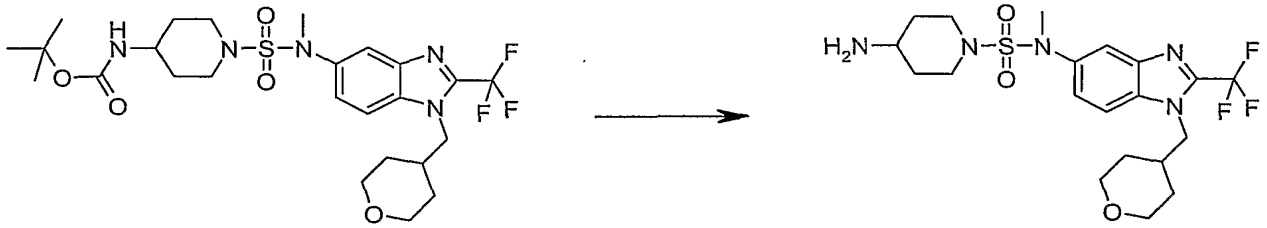
Step A. 4-{[(Cyclopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide



A solution of isocyanatocyclopropane in THF (1 mmol) (freshly prepared from cyclopropylamine and triphosgene) was added to a solution of 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide (38 mg, 0.08 mmol) (see following step B for preparation) in THF (3 mL) at room temperature. The mixture was stirred for 1 h. After evaporation, the crude product was purified by MPLC using EtOAc/MeOH

(20:1) on silica gel to give 45 mg (100%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 0.34 - 0.47 (m, 2 H), 0.59 - 0.71 (m, 2 H), 1.33 - 1.53 (m, 6 H), 1.77 - 1.87 (m, 2 H), 2.16 - 2.30 (m, 1 H), 2.36 - 2.46 (m, 1 H), 2.83 - 2.94 (m, 2 H), 3.28 (s, 3 H), 3.30 - 3.37 (m, 2 H), 3.51 - 3.59 (m, 1 H), 3.58 - 3.68 (m, 2 H), 3.82 - 3.95 (m, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.57 (dd, J=8.89, 2.05 Hz, 1 H), 7.76 (d, J=8.98 Hz, 1 H), 7.83 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ = 559.0; Anal. Calcd for $C_{24}H_{33}N_6O_4SF_3$+0.60 TFA+ 0.30 H_2O + 0.10 CH3OH (635.65): C, 47.81; H, 5.49; N, 13.22; Found: C, 47.83; H, 5.45; N, 13.20.

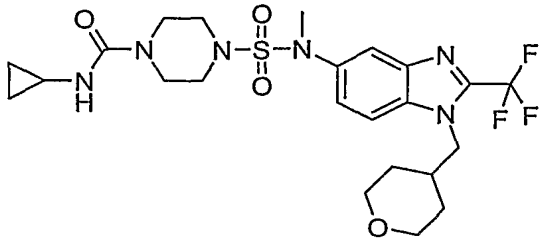
Step B. 4-Amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide



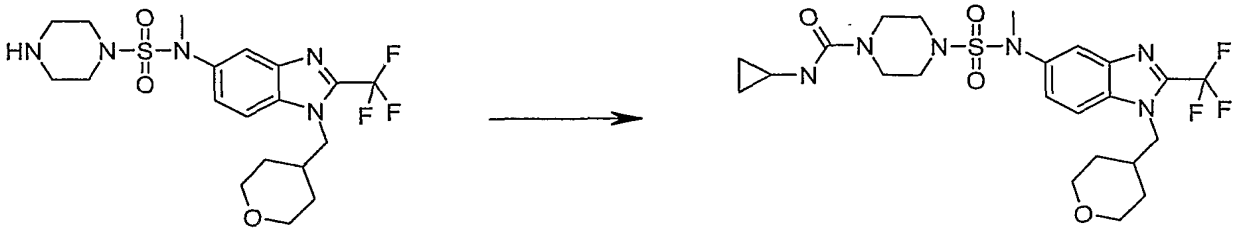
TFA (3 mL) was added to a solution of *tert*-butyl [1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]carbamate (210 mg, 0.365 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred for 1 h. Upon evaporation, the residue was dissolved in DCM (50 mL), washed with 2*N* NaOH (2x5 mL), brine (5 mL) and dried over Na_2SO_4. After concentration, 168 mg (97%) of a white solid was obtained the title compound. MS (ESI) $(M+H)^+$ = 475.99.

Example 52

***N*-Cyclopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide**

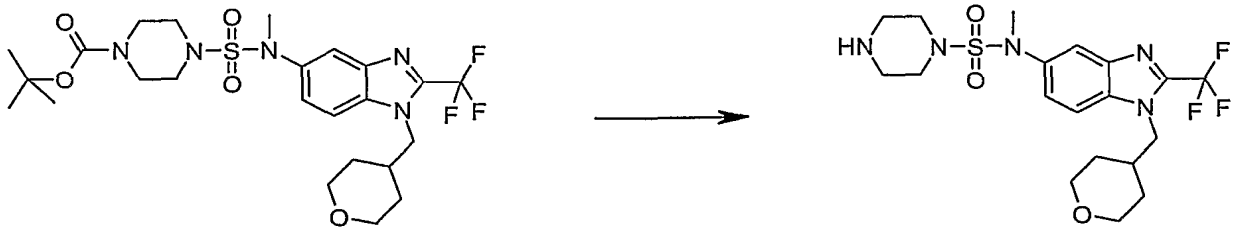


Step A. *N*-Cyclopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide



Following the procedure in Step A of Example 51, using *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide (38 mg, 0.083 mmol) (see following step B for preparation) and a solution of isocyanatocyclopropane in THF (1 mmol). The crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 45 mg (99%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 0.39 - 0.44 (m, 2 H), 0.60 - 0.68 (m, 2 H), 1.44 - 1.47 (m, 4 H), 2.19 - 2.35 (m, 1 H), 2.47 - 2.55 (m, 1 H), 3.13 - 3.22 (m, 4 H), 3.32 (s, 3 H), 3.32 - 3.38 (m, 6 H), 3.86 - 3.99 (m, 2 H), 4.33 (d, J=7.81 Hz, 2 H), 7.59 (dd, J=8.89, 2.05 Hz, 1 H), 7.79 (d, J=8.98 Hz, 1 H), 7.86 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ = 545.0; Anal. Calcd for $C_{23}H_{31}F_3N_6O_4S$+0.70 TFA(624.42): C, 46.94; H, 5.12; N, 13.46; Found: C, 46.90; H, 4.65; N, 13.45.

Step B. *N*-Methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide

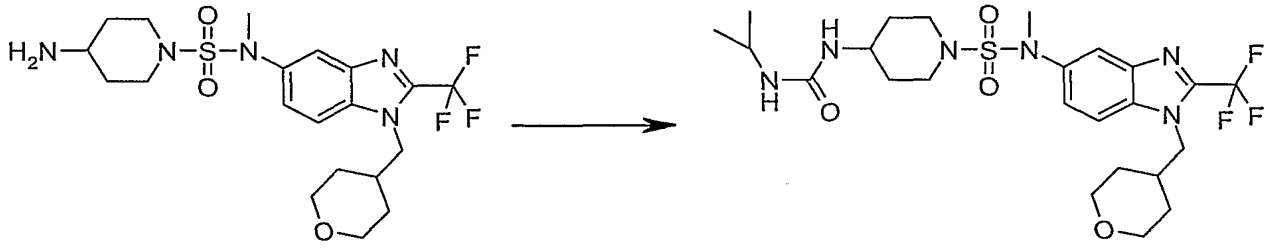


Following the procedure in Step B of Example 51, *tert*-butyl 4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxylate (234 mg, 0.417 mmol) was treated with

TFA (3 mL) in DCM (3 mL). 176 mg (91%) of a white solid was obtained as the title compound. MS (ESI) $(M+H)^+$ = 461.96.

Example 53

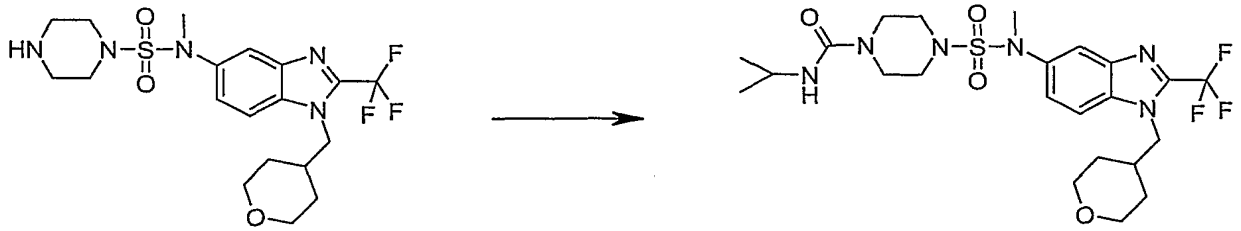
4-{[(Isopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide



Following the procedure in Step A of Example 51, using 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide (38 mg, 0.08 mmol) and 2-isocyanatopropane (0.2 mL) in THF (3 mL). The crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 38 mg (85%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.07 (d, J=6.45 Hz, 6 H), 1.29 - 1.40 (m, 2 H), 1.40 - 1.53 (m, 4 H), 1.78 - 1.87 (m, 2 H), 2.17 - 2.31 (m, 1 H), 2.85 - 2.95 (m, 2 H), 3.28 (s, 3 H), 3.30 - 3.37 (m, 2 H), 3.48 - 3.56 (m, 1 H), 3.56 - 3.66 (m, 2 H), 3.68 - 3.81 (m, 1 H), 3.85 - 3.98 (m, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.57 (dd, J=8.89, 2.05 Hz, 1 H), 7.76 (d, J=8.98 Hz, 1 H), 7.83 (d, J=1.56 Hz, 1 H); MS (ESI) $(M+H)^+$ = 561.0; Anal. Calcd for $C_{24}H_{35}F_3N_6O_4S$+0.70 TFA+ (640.46): C, 47.63; H, 5.62; N, 13.12; Found: C, 47.64; H, 5.51; N, 13.26.

Example 54

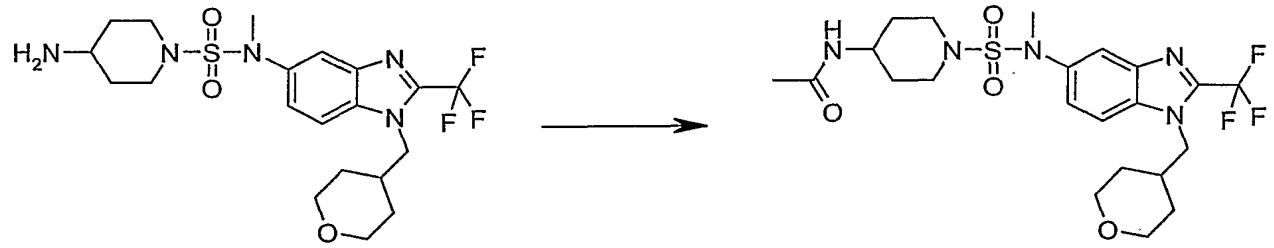
***N*-Isopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide**



Following the procedure in Step A of Example 51, using *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide (40 mg, 0.087 mmol) and 2-isocyanatopropane (0.2 mL) in THF (3 mL). The crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 48 mg (100%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.09 (d, J=6.45 Hz, 6 H), 1.38 - 1.53 (m, 4 H), 2.15 - 2.34 (m, 1 H), 3.14 - 3.21 (m, 4 H), 3.31 (s, 3 H), 3.33 - 3.40 (m, 6 H), 3.78 - 3.87 (m, 1 H), 3.87 - 3.95 (m, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.58 (dd, J=8.89, 2.05 Hz, 1 H), 7.77 (d, J=8.79 Hz, 1 H), 7.85 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+ = 547.0$; Anal. Calcd for $C_{23}H_{33}F_3N_6O_4S$+0.50 TFA+ 0.20 H_2O + 0.40 CH_3OH (613.64): C, 47.37; H, 5.70; N, 13.70; Found: C, 47.41; H, 5.62; N, 13.65.

Example 55

***N*-[1-({Methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]acetamide**

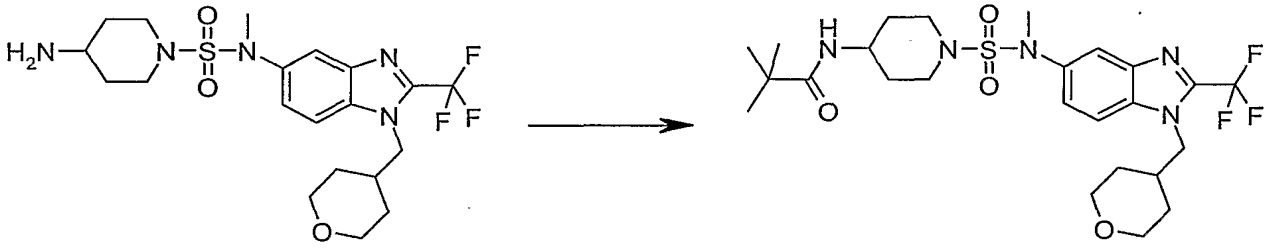


Acetyl chloride (9 mg, 0.11 mmol) was added to a solution of 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide (45 mg, 0.094 mmol) and triethylamine (12 mg, 0.12 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred for 3 h at room temperature. After evaporation, the crude product was purified by MPLC using EtOAc/MeOH (10:1) on silica gel to give 49 mg (100%) of a white solid as the title compound.

^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.36 - 1.55 (m, 6 H), 1.79 - 1.87 (m, 2 H), 1.90 (s, 3 H), 2.19 - 2.33 (m, 1 H), 2.86 - 2.96 (m, 2 H), 3.30 (s, 3 H), 3.32 - 3.38 (m, 2 H), 3.63 - 3.70 (m, 2 H), 3.70 - 3.78 (m, 1 H), 3.89 - 3.96 (m, 2 H), 4.33 (d, J=7.62 Hz, 2 H), 7.59 (dd, J=8.89, 2.05 Hz, 1 H), 7.78 (d, J=8.98 Hz, 1 H), 7.85 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ = 518.0 Anal. Calcd for $C_{22}H_{30}F_3N_5O_4S$+0.60 TFA+ 0.10 CH_3OH (589.19): C, 47.50; H, 5.30; N, 11.89; Found: C, 47.61; H, 5.32; N, 11.82.

Example 56

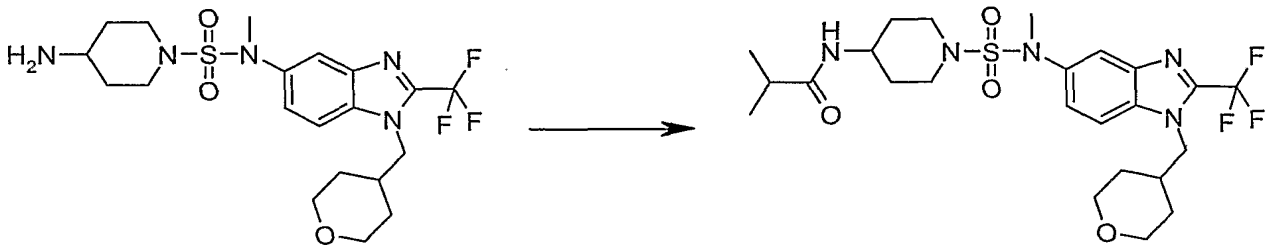
2,2-Dimethyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide



Following the procedure in Example 55, using 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide (45 mg, 0.094 mmol), 2,2-dimethylpropanoyl chloride (14 mg, 0.11 mmol) was and triethylamine (12 mg, 0.12 mmol) in DCM (5 mL). The crude product was purified by MPLC using EtOAc/Hex (2:1) on silica gel to give 44 mg (84%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.12 (s, 9 H), 1.38 - 1.56 (m, 6 H), 1.75 - 1.78 (m, 2 H), 2.14 - 2.34 (m, 1 H) 2.80 - 2.90 (m, 2 H), 3.28 (s, 3 H), 3.30 - 3.39 (m, 2 H), 3.61 - 3.79 (m, 3 H), 3.86 - 3.98 (m, 2 H), 4.32 (d, J=7.62 Hz, 2 H), 7.57 (dd, J=8.98, 1.95 Hz, 1 H), 7.76 (d, J=8.79 Hz, 1 H), 7.84 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ = 560.0; Anal. Calcd for $C_{25}H_{36}F_3N_5O_4S$+0.50 TFA (616.67): C, 50.64; H, 5.97; N, 11.36; Found: C, 50.76; H, 5.99; N, 11.37.

Example 57

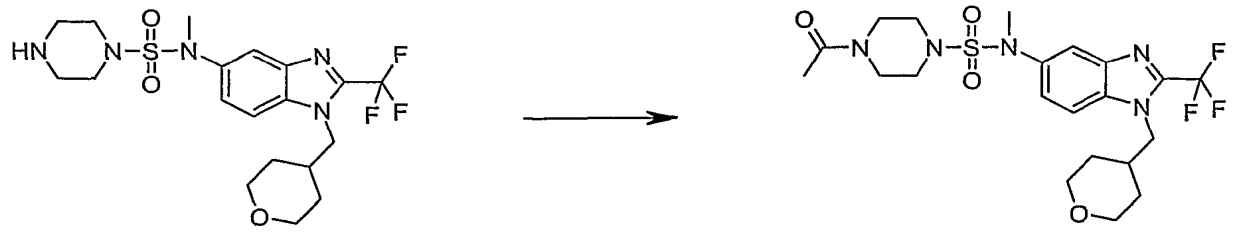
2-Methyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide



Following the procedure in Example 55, using 4-amino-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide (45 mg, 0.094 mmol), 2-methylpropanoyl chloride (11 mg, 0.11 mmol) was and triethylamine (12 mg, 0.12 mmol) in DCM (5 mL) The crude product was purified by MPLC using EtOAc/Hex (2:1) on silica gel to give 46 mg (89%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.05 (d, J=6.84 Hz, 6 H), 1.35 - 1.54 (m, 6 H), 1.76 - 1.86 (m, 2 H), 2.17 - 2.30 (m, 1 H), 2.32 - 2.44 (m, 1 H), 2.83 - 2.95 (m, 2 H), 3.28 (s, 3 H), 3.29 - 3.37 (m, 2 H), 3.58 - 3.76 (m, 3 H), 3.85 - 3.98 (m, 2 H), 4.31 (d, J=7.42 Hz, 2 H), 7.57 (dd, J=8.89, 2.05 Hz, 1 H) 7.76 (d, J=8.98 Hz, 1 H), 7.83 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ = 546.0; Anal. Calcd for $C_{24}H_{34}F_3N_5O_4S$+0.10 TFA (557.03): C, 52.18; H, 6.17; N, 12.57; Found: C, 52.44; H, 6.03; N, 12.44.

Example 58

4-Acetyl-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide



Following the procedure in Example 55, using *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide (43

mg, 0.096 mmol), triethylamine (12 mg, 0.12 mmol) and acetyl chloride (9 mg, 0.12 mmol) in DCM (5 mL) .The crude product was purified by MPLC using EtOAc/MeOH (20:1) on silica gel to give 45 mg (92%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.39 - 1.52 (m, 4 H), 2.06 (s, 3 H), 2.17 - 2.33 (m, 1 H), 3.17 - 3.27 (m, 4 H), 3.31 (s, 3 H), 3.32 - 3.36 (m, 2 H), 3.49 - 3.59 (m, 4 H), 3.86 - 3.96 (m, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.58 (dd, J=8.79, 2.15 Hz, 1 H), 7.77 (d, J=8.98 Hz, 1 H), 7.85 (d, J=1.76 Hz, 1 H); MS (ESI) $(M+H)^+$ = 504.0; Anal. Calcd for $C_{21}H_{28}F_3N_5O_4S$+0.60 TFA +0.10 CH_3OH (575.17): C, 46.57; H, 5.08; N, 12.18; Found: C, 46.67; H, 5.13; N, 12.16.

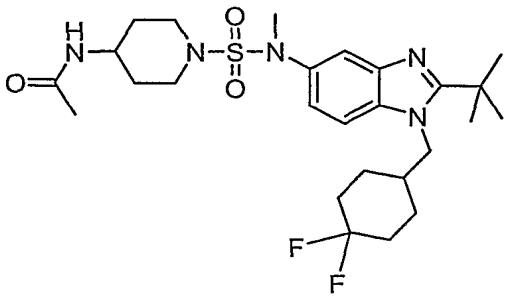
Example 59

4-(2,2-Dimethylpropanoyl)-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide

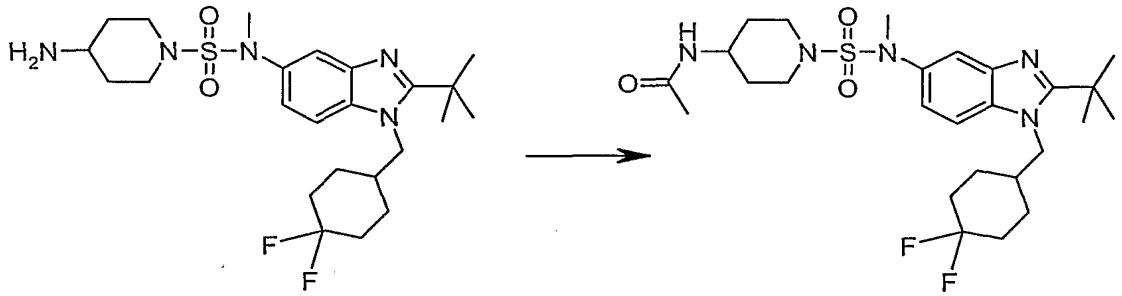
Following the procedure in Example 55, using *N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide (43 mg, 0.096 mmol), triethylamine (12 mg, 0.12 mmol) and 2,2-dimethylpropanoyl chloride (14 mg, 0.12 mmol) in DCM (5 mL). The crude product was purified by MPLC using EtOAc/Hex(2:1) on silica gel to give 51 mg (97%) of a white solid as the title compound. ^{1}HNMR (400 MHz, METHANOL-D_4): δ 1.22 (s, 9 H), 1.40 - 1.54 (m, 4 H), 2.17 - 2.31 (m, 1 H), 3.17 - 3.23 (m, 4 H), 3.30 - 3.36 (m, 2 H), 3.31 (s, 3 H), 3.61 - 3.68 (m, 4 H), 3.86 - 3.95 (m, 2 H), 4.31 (d, J=7.62 Hz, 2 H), 7.58 (dd, J=8.89, 2.05 Hz, 1 H), 7.77 (d, J=8.79 Hz, 1 H), 7.85 (d, J=1.95 Hz, 1 H); MS (ESI) $(M+H)^+$ = 546.0; Anal. Calcd for $C_{24}H_{34}F_3N_5O_4S$+0.30 TFA +0.20 CH_3OH (586.24): C, 50.81; H, 6.03; N, 11.95; Found: C, 50.81; H, 5.99; N, 11.90.

Example 60

***N*-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide**

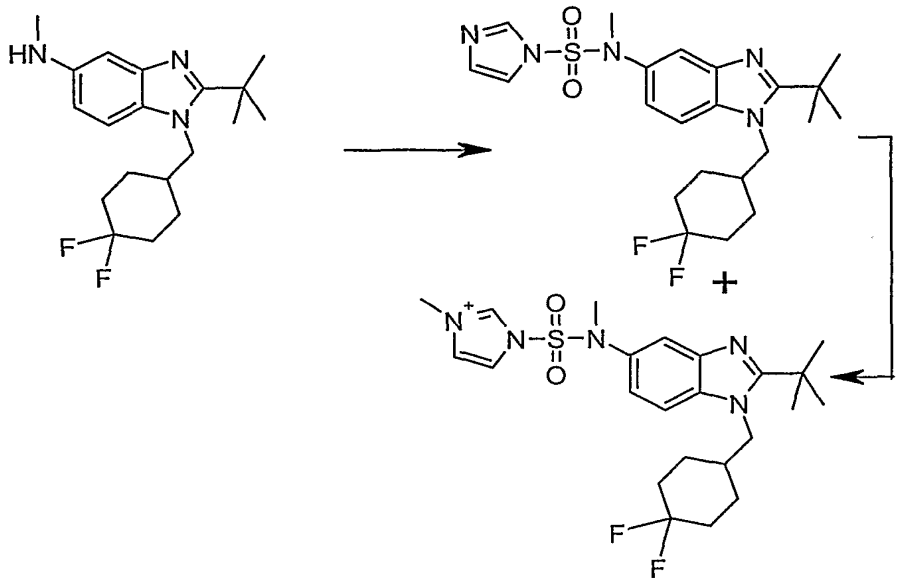


Step A. *N*-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide



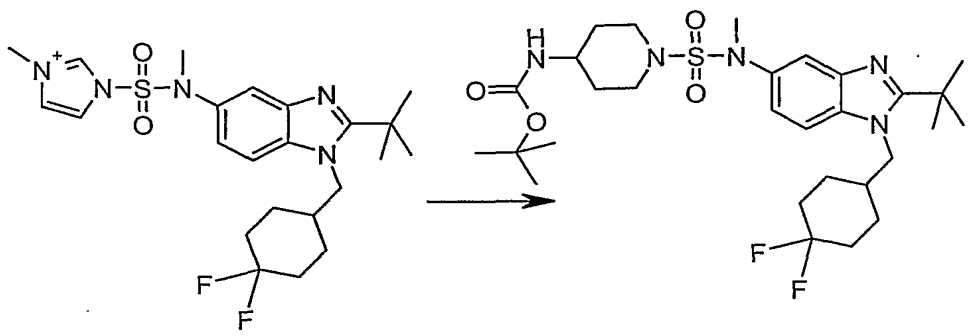
Acetic anhydride (2.0 mmol) was added into a solution of triethylamine (2.0 mmol) and 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide (crude product from step D, 0.9 mmol) in CH_2Cl_2 (20 mL). After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then purified by silica gel chromatography (AcOEt to MeOH/AcOEt (1:9)) to give *N*-(1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide as a solid (235 mg, 48 % for steps A-D). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.28 (m, 2H), 1.40-1.76 (m, 8H), 1.64 (s, 9H), 1.88 (s, 3H), 2.04 (m, 2H), 2.24 (m, 1H), 2.90 (m, 2H), 3.28 (s, 3H), 3.68 (m, 3H), 4.50 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H).

Step B. 1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate



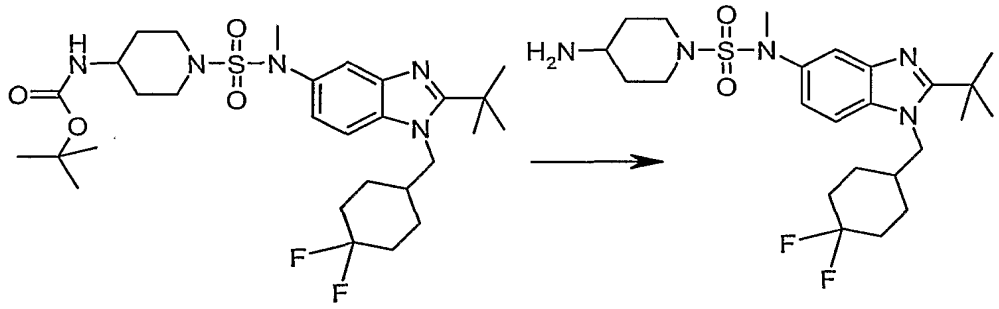
3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium triflate (508 mg; 1.4 mmol) was added into a solution of 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (300 mg, 0.9 mmol) in acetonitrile (10 mL). After being stirred at room temperature for 2 hr, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with brine, and dried over Na_2SO_4. After removing of solvents provided a mixture (1:1) of *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide and 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate, which was dissolved in dichloromethane (10 mL). The resulting solution was treated with methyl trifluoromethanesulfonate (0. 5 mmol) at 0^0C for 2 hr. The reaction mixture was then concentrated under reduced pressure to give 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate as a solid, which was used in the step C without any purification.

Step C. *tert*-Butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate



A solution of Hunig's base (1.0 mmol), 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (crude product from Step B, 0.9 mmol) and *tert*-butyl piperidin-4-ylcarbamate (200 mg, 1.0 mmol) in MeCN (20 mL) was heated for 1 hr at 80^{0}C. The reaction mixture was then concentrated under reduced pressure to give crude *tert*-butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate as a solid, which was used directly in Step D.

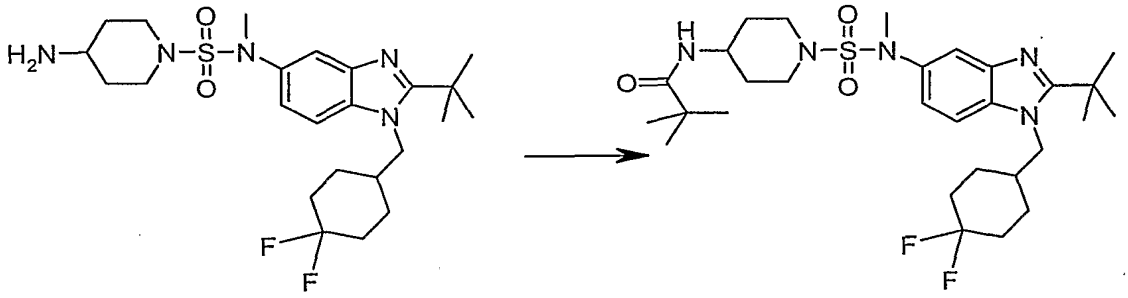
Step D. 4-Amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide



A solution of *tert*-butyl (1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)carbamate (crude product from Step C, 0.9 mmol) in 10 mL CH_2Cl_2 was treated with 10 mL TFA at room temperature. After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with Na_2CO_3 solution and brine, and dried over Na_2SO_4. fter removing of solvents provided the crude 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide, which was used in Step A without purification.

Example 61

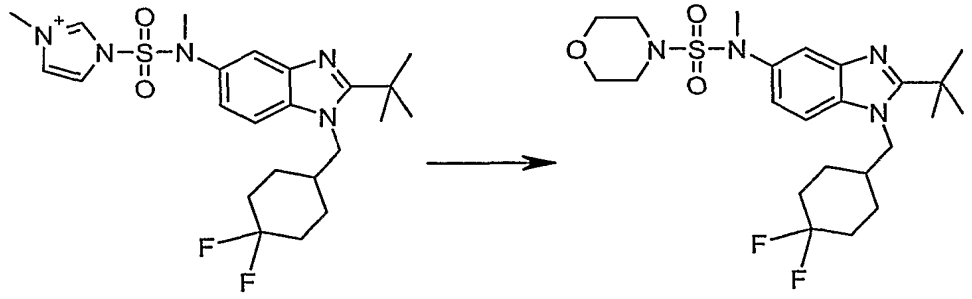
***N*-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide**



Following the procedure in Step A of Example 60, 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide (50 mg, 0.1 mmol) was reacted with 2,2-dimethylpropanoyl chloride (24 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-(1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide (TFA salt, 7 mg, 10 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.13 (s, 9H), 1.28 (m, 2H), 1.53 (m, 3H), 1.64 (s, 9H), 1.76 (m, 5H), 2.04 (m, 2H), 2.24 (m, 1H), 2.87 (m, 2H), 3.28 (s, 3H), 3.68 (m, 3H), 4.50 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.77 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 582.0.

Example 62

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylmorpholine-4-sulfonamide**

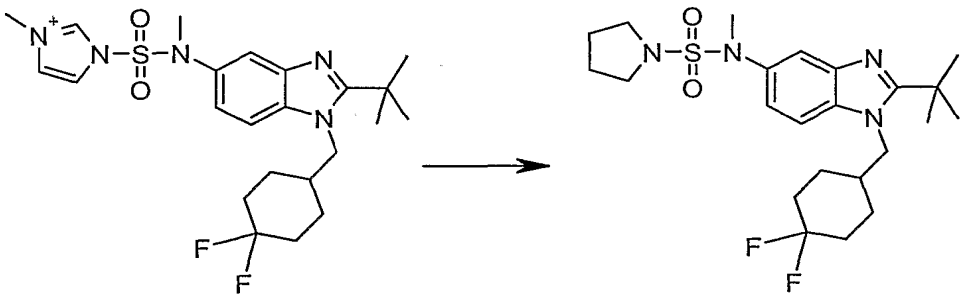


Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-

methyl-1*H*-imidazol-3-ium triflate (0.1 mmol) was reacted with morpholine (35 mg, 0.4 mmol), after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylmorpholine-4-sulfonamide (TFA salt, 56 mg, 93 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.64 (s, 9H), 2.04 (m, 2H), 2.24 (m, 1H), 3.19 (m, 4H), 3.33 (s, 3H), 3.62 (m, 4H), 4.50 (d, J = 7.4 Hz, 2H), 7.61(d, J=9.0 Hz, 1H), 7.79 (s, 1H), 7.87(d, J=9.0 Hz, 1H).

Example 63

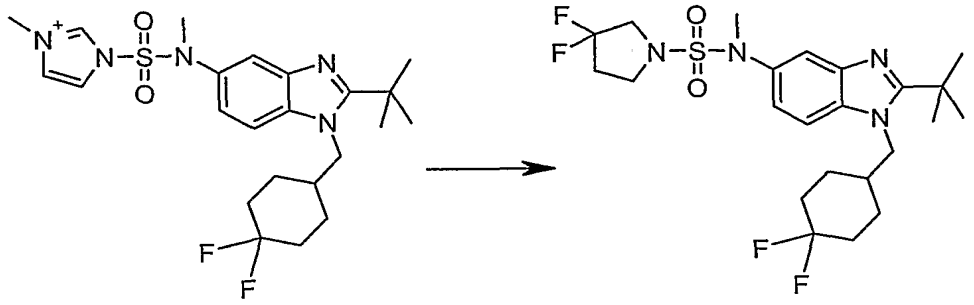
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpyrrolidine-1-sulfonamide



Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (0.1 mmol) was reacted with pyrrolidine (28 mg, 0.4 mmol), after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpyrrolidine-1-sulfonamide (TFA salt, 26 mg, 48 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.23 (m, 2H), 1.40-1.76 (m, 6H), 1.64 (s, 9H), 1.86 (m, 2H), 2.01 (m, 2H), 2.24 (m, 1H), 3.04 (m, 2H), 3.27 (m, 2H), 3.28(s, 3H), 4.49 (d, J = 7.4 Hz, 2H), 7.58(d, J=9.0 Hz, 1H), 7.77 (s, 1H), 7.84(d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 469.0.

Example 64

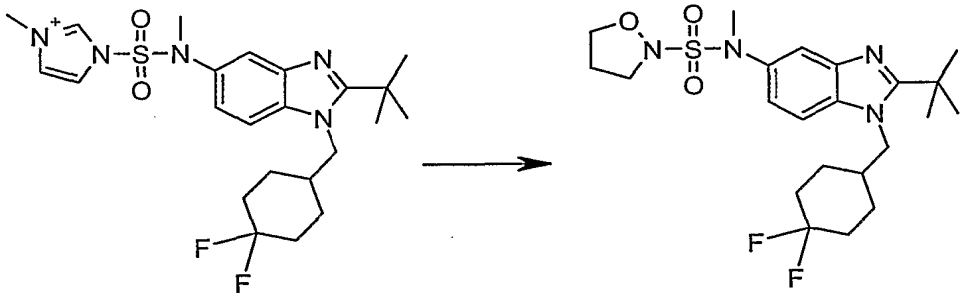
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-3,3-difluoro-*N*-methylpyrrolidine-1-sulfonamide



Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (0.1 mmol) was reacted with 3,3-difluoropyrrolidine (42 mg, 0.4 mmol), after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-3,3-difluoro-*N*-methylpyrrolidine-1-sulfonamide (TFA salt, 18 mg, 26 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.64 (s, 9H), 2.04 (m, 2H), 2.24 (m, 1H), 2.38 (m, 2H), 3.32 (s, 3H), 3.52 (m, 2H), 3.60 (m, 2H), 4.50 (d, J = 7.4 Hz, 2H), 7.59(d, J=9.0 Hz, 1H), 7.77 (s, 1H), 7.86(d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 505.0.

Example 65

***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylisoxazolidine-2-sulfonamide**

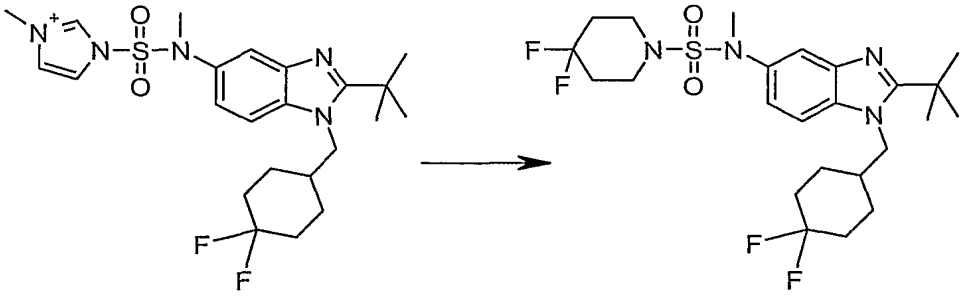


Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (0.1 mmol) was reacted with isoxazolidine hydrochloride (44 mg, 0.4 mmol) and Hunig's base (1.0 mL), , after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylisoxazolidine-2-

sulfonamide (TFA salt, 58 mg, 99 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.64 (s, 9H), 2.04 (m, 2H), 2.31 (m, 1H), 2.33 (m, 2H), 3.44 (s, 3H), 3.55 (m, 2H), 4.11 (m, 2H), 4.51 (d, J = 7.4 Hz, 2H), 7.60 (m, 1H), 7.87 (m, 2H); MS (ESI) $(M+H)^+$ 471.0.

Example 66

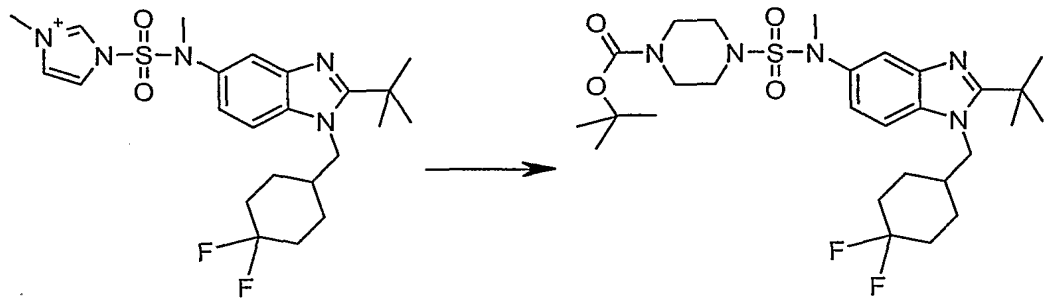
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4,4-difluoro-*N*-methylpiperidine-1-sulfonamide**



Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (0.1 mmol) was reacted with 4,4-difluoropiperidine hydrochloride (62 mg, 0.4 mmol) and Hunig's base (1.0 mL), , after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4,4-difluoro-*N*-methylpiperidine-1-sulfonamide (TFA salt, 36 mg, 57 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.64 (s, 9H), 1.97 (m, 6H), 2.24 (m, 1H), 3.31 (s, 3H), 3.38 (m, 4H), 4.50 (m, 2H), 7.60(d, J=9.0 Hz, 1H), 7.78 (s, 1H), 7.87(d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 519.0.

Example 67

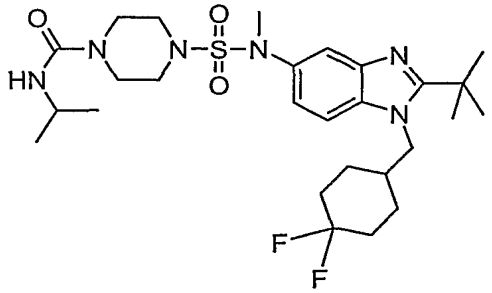
***tert*-Butyl 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperazine-1-carboxylate**



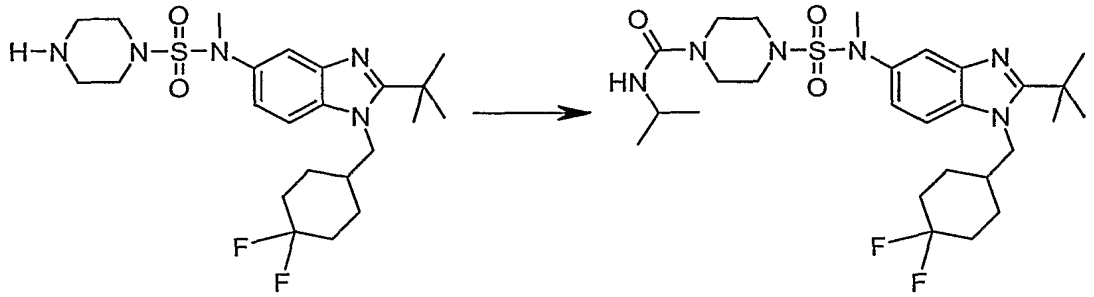
Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (2.0 mmol) was reacted with *tert*-butyl piperazine-1-carboxylate (930 mg, 5.0 mmol) and Hunig's base (1.0 mL), after being purified by silica gel chromatography, to provide *tert*-butyl 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperazine-1-carboxylate (730 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 1.46 (m, 3H), 1.51 (s, 9H), 1.67 (m, 3H), 2.09 (m, 3H), 3.12 (m, 4H), 3.25 (s, 3H), 3.35 (m, 4H), 4.16 (m, 2H), 7.22 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.67 (s, 1H); MS (ESI) $(M+H)^+$ 584.0.

Example 68

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide

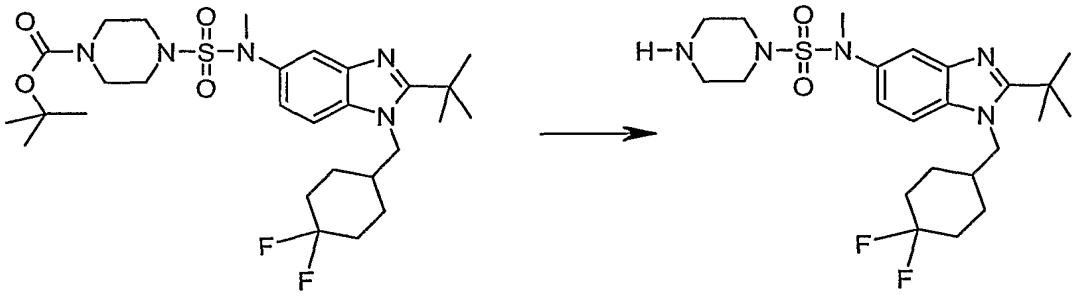


Step A. 4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide



Isopropyl isocyanate (85 mg, 1.0 mmol) was added into a solution of triethylamine (1.0 mmol) and *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide (100 mg, 0.21 mmol) in CH_2Cl_2 (10 mL). After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then purified by silica gel chromatography (Hexane to AcOEt) to give 4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide (114 mg, TFA salt, 81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J=6.5 Hz, 6H), 1.52 (m, 3H), 1.56 (s, 9H), 1.72 (m, 3H), 2.14 (m, 3H), 3.20 (m, 4H), 3.30 (s, 3H), 3.35 (m, 4H), 3.94 (m, 1H), 4.22 (m, 2H), 4.35 (m, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 569.0.

Step B. *N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide

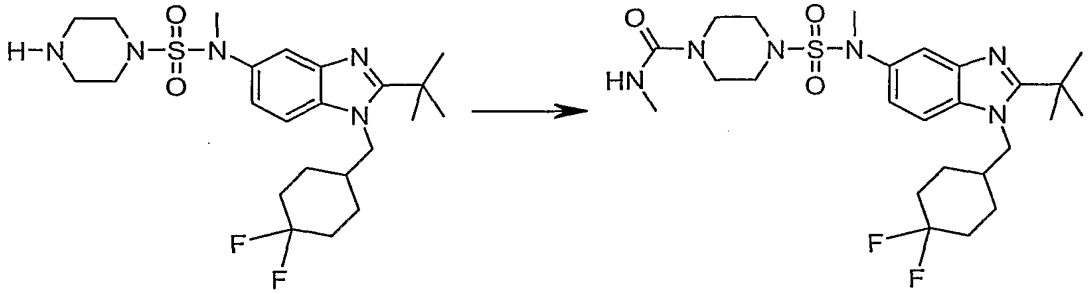


A solution of *tert*-butyl 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperazine-1-carboxylate (720 mg, 1.23 mmol) in 10 mL CH_2Cl_2 was treated with 10 mL TFA at room temperature. After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with Na_2CO_3 solution and brine, and dried over Na_2SO_4. Removal of solvents

provided crude *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide (434 mg, 73 %), which was used in Step A without purification.

Example 69

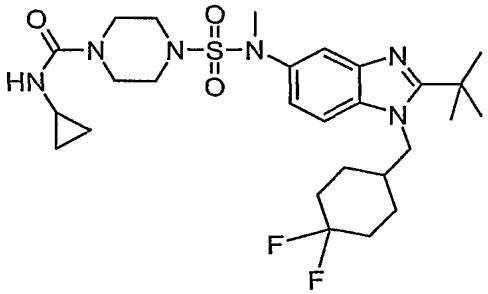
4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide



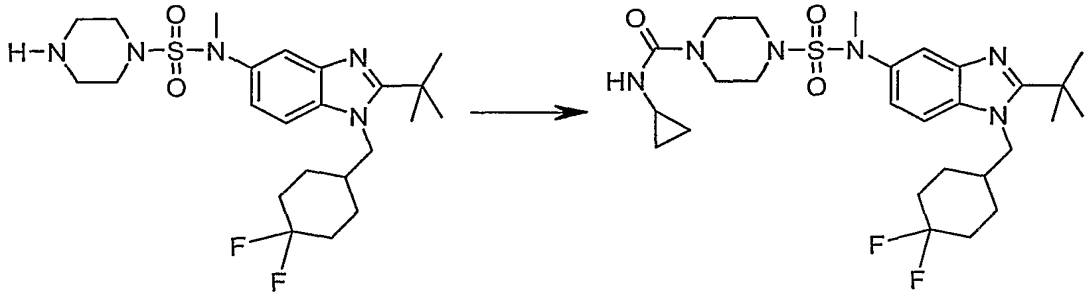
Following the procedure in Step A of Example 68, *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide (56 mg, 0.116 mmol) was reacted with methyl isocyanate (57 mg, 1.0 mmol), after being purified by silica gel chromatography, to provide 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide (TFA salt, 49 mg, 64 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 3H), 1.50 (s, 9H), 1.67 (m, 3H), 2.10 (m, 3H), 2.71 (m, 3H), 3.14 (m, 4H), 3.23 (s, 3H), 3.31 (m, 4H), 4.16 (d, J = 7.4 Hz, 2H), 4.68 (m, 1H), 7.22 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 8.6 Hz, 1H), 7.65 (s, 1H); MS (ESI) $(M+H)^+$ 541.0.

Example 70

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide

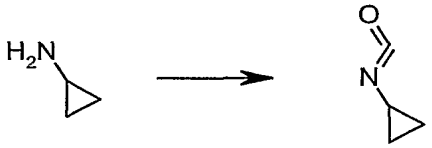


Step A. 4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide (54 mg, 0.112 mmol) was reacted with cyclopropyl isocyanate (1.0 mmol), after being purified by silica gel chromatography, to provide 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide (TFA salt, 48 mg, 63 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (m, 1H), 0.54 (m, 1H), 0.72 (m, 2H), 1.54 (m, 2H), 1.56 (s, 9H), 1.72 (m, 3H), 2.14 (m, 3H), 2.50 (m, 1H), 2.60 (m, 1H), 3.18 (m, 4H), 3.29 (s, 3H), 3.34 (m, 4H), 4.22 (d, J = 7.4 Hz, 2H), 5.01 (m, 1H), 7.28 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.71 (s, 1H); MS (ESI) $(M+H)^+$ 567.0.

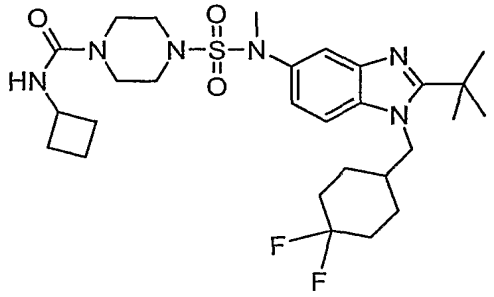
Step B. Cyclopropyl isocyanate



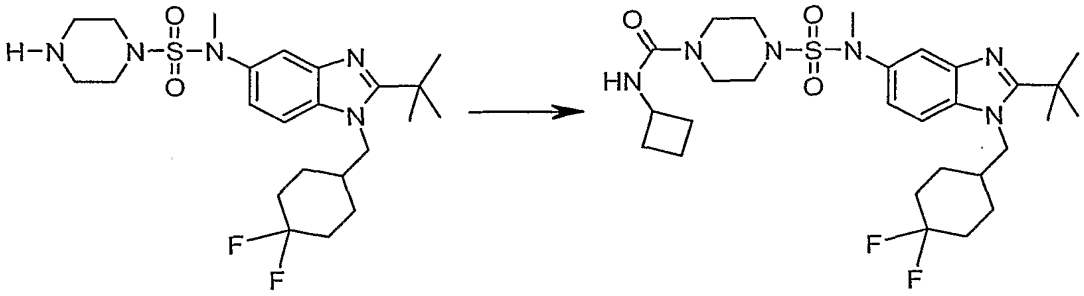
A solution of cyclopropylamine (57 mg, 1.0 mmol) and DIPEA (3.0 mmol) in 5 mL THF was slowly added to a solution of triphosgene (105 mg, 0.35 mmol) in 10 mL THF at 0^0C. After 30 min, the cyclopropyl isocyanate solution was used directly in Step A.

Example 71

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide

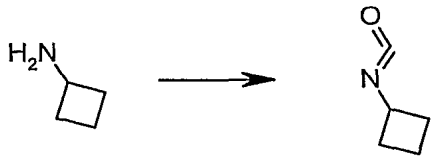


Step A. 4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperazine-1-sulfonamide (58 mg, 0.12 mmol) was reacted with cyclobutyl isocyanate (1.0 mmol), after being purified by silica gel chromatography, to provide 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide (TFA salt, 39 mg, 47 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (m, 2H), 1.56 (s, 9H), 1.72 (m, 8H), 2.04 (m, 3H), 2.32 (m, 2H), 3.19 (m, 4H), 3.30 (s, 3H), 3.34 (m, 4H), 4.21 (m, 2H), 4.25 (m, 1H), 4.65 (m, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 581.0.

Step B: Cyclobutyl isocyanate

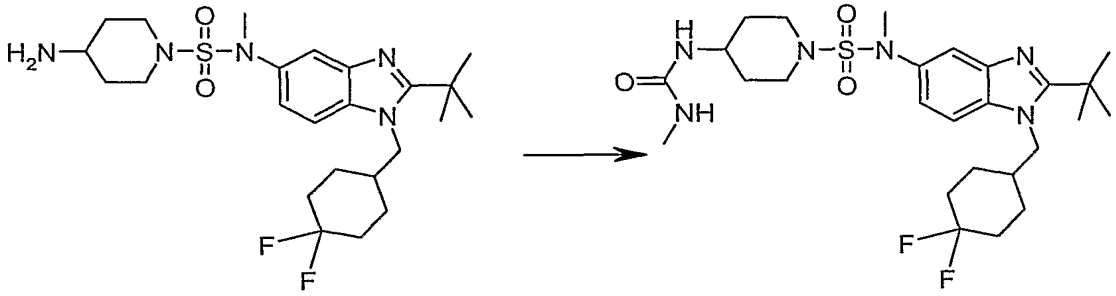


A solution of cyclobutylamine (71 mg, 1.0 mmol) and DIPEA (3.0 mmol) in 5 mL THF was slowly added to a solution of triphosgene (105 mg, 0.35 mmol) in 10 mL

THF at 0°C. After 30 min, the cyclopropyl isocyanate solution was used directly in Step A.

Example 72

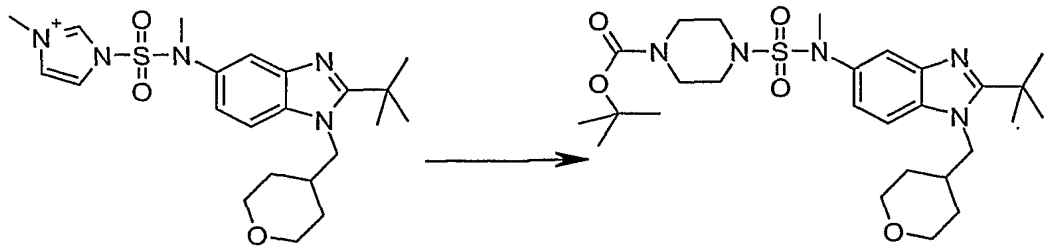
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-4-{[(methylamino)carbonyl]amino}piperidine-1-sulfonamide**



Following the procedure in Step A of Example 68, 4-amino-*N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide (50 mg, 0.1 mmol) was reacted with methyl isocyanate (57 mg, 1.0 mmol), after being purified by silica gel chromatography, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-4-{[(methylamino)carbonyl]amino}piperidine-1-sulfonamide (TFA salt, 49 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (m, 2H), 1.52 (m, 3H), 1.56 (s, 9H), 1.72 (m, 3H), 1.89 (m, 2H), 2.15 (m, 3H), 2.72 (s, 3H), 2.83 (m, 2H), 3.27 (s, 3H), 3.63 (m, 3H), 4.22 (d, J = 8.0 Hz, 2H), 5.15 (m, 1H), 7.30 (m, 2H), 7.71 (s, 1H); MS (ESI) $(M+H)^+$ 555.0.

Example 73

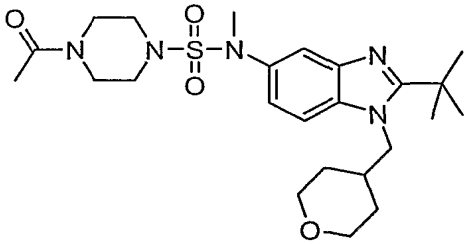
***N*-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide**



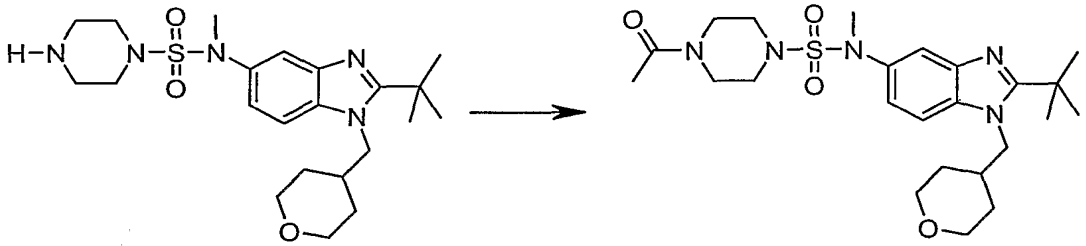
Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (500 mg, 0.84 mmol) was reacted with *tert*-butyl piperazine-1-carboxylate (558 mg, 3.0 mmol), after being purified by silica gel chromatography, to provide *tert*-butyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate (460 mg, 100 %). MS (ESI) $(M+H)^+$ 550.0.

Example 74

4-Acetyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide

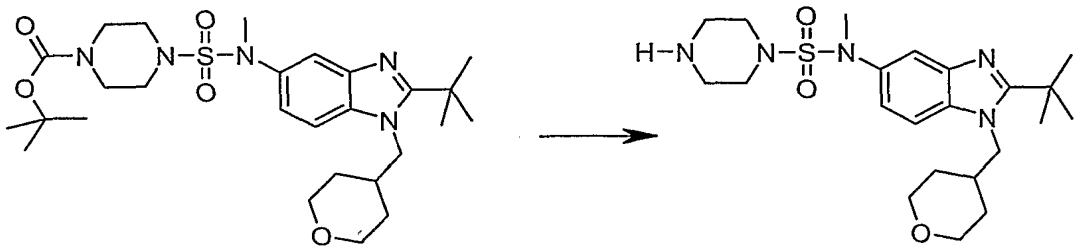


Step A. 4-Acetyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide trifluoroacetate (100 mg, 0.18 mmol) was reacted with acetyl chloride (79 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide 4-acetyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (TFA salt, 58 mg, 53 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.54 (m, 4H), 1.66 (s, 9H), 2.07 (s, 3H), 2.36 (m, 1H), 3.20 (m, 2H), 3.33 (s, 3H), 3.34 (m, 4H), 3.55 (m, 4H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 7.65 (d, J=9.0 Hz, 1H), 7.79 (s, 1H), 7.92 (d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 492.0.

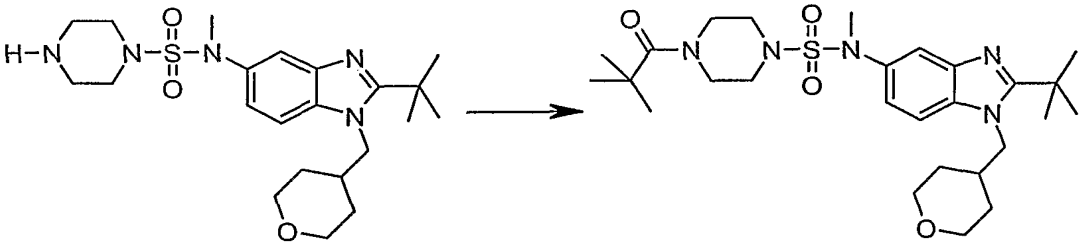
Step B: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide



A solution of *tert*-butyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate (460 mg, 0.84 mmol) in 10 mL CH_2Cl_2 was treated with 10 mL TFA at room temperature. After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (TFA salt, 100 %), which was used in Step A without purification.

Example 75

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(2,2-dimethylpropanoyl)-*N*-methylpiperazine-1-sulfonamide**

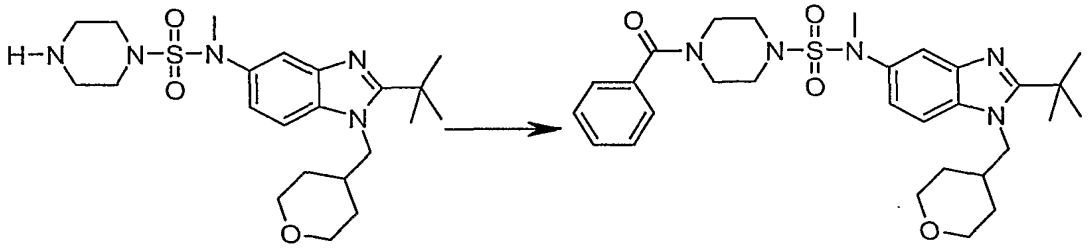


Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide trifluoroacetate (100 mg, 0.18 mmol) was reacted with 2,2-dimethylpropanoyl chloride (120 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(2,2-dimethylpropanoyl)-*N*-methylpiperazine-1-sulfonamide (TFA salt, 24 mg, 21 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.23 (s, 9H), 1.56 (m, 4H), 1.66 (s, 9H), 2.36 (m, 1H), 3.23 (m, 4H), 3.33 (s, 3H), 3.36 (m, 2H), 3.66 (m, 4H), 3.91 (m, 2H), 4.51

(d, J = 7.6 Hz, 2H), 7.65 (d, J=9.2 Hz, 1H), 7.79 (s, 1H), 7.92 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$ 534.0.

Example 76

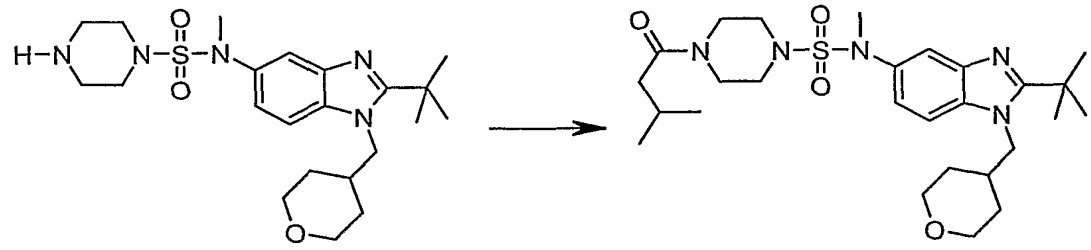
4-Benzoyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (45 mg, 0.10 mmol) was reacted with benzoyl chloride (28 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide 4-benzoyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (TFA salt, 64 mg, 96 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.58 (m, 4H), 1.67 (s, 9H), 2.36 (m, 1H), 3.28 (m, 6H), 3.33 (s, 3H), 3.47 (m, 2H), 3.74 (m, 2H), 3.92 (m, 2H), 4.52 (d, J = 7.6 Hz, 2H), 7.40 (m, 2H), 7.46 (m, 3H), 7.68 (d, J=9.0 Hz, 1H), 7.80 (s, 1H), 7.95 (d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 554.0.

Example 77

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(3-methylbutanoyl)piperazine-1-sulfonamide**

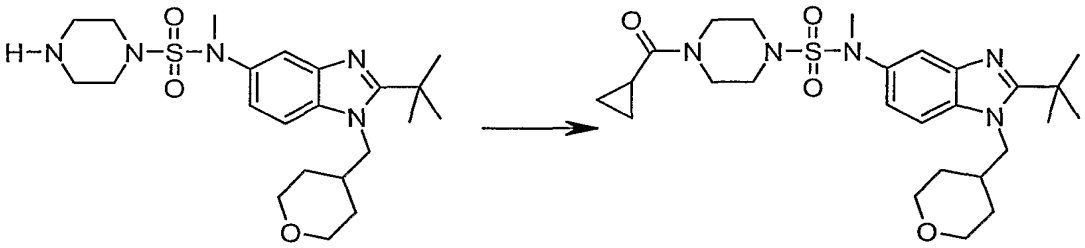


Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (45 mg, 0.10 mmol) was reacted with 3-methylbutanoyl chloride (24 mg, 0.2 mmol), after

being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(3-methylbutanoyl)piperazine-1-sulfonamide (TFA salt, 63 mg, 97 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 0.87 (d, J=7.4 Hz, 6H), 1.45 (m, 4H), 1.49 (s, 9H), 2.00 (m, 1H), 2.09 (d, J=6.9 Hz, 2H), 2.22 (m, 1H), 3.06 (m, 2H), 3.16 (m, 2H), 3.22 (s, 3H), 3.23 (m, 2H), 3.39 (m, 2H), 3.52 (m, 2H), 3.91 (m, 2H), 4.12 (d, J = 7.6 Hz, 2H), 4.83 (m, 1H), 7.23 (m, 2H), 7.64 (s, 1H); MS (ESI) $(M+H)^+$ 534.0.

Example 78

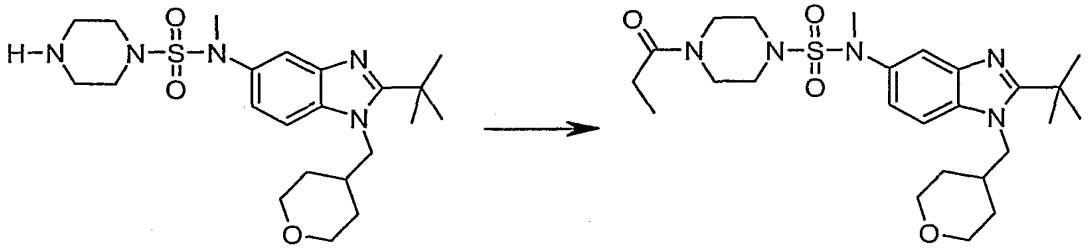
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclopropylcarbonyl)-*N*-methylpiperazine-1-sulfonamide



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with cyclopropanecarbonyl chloride (21 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclopropylcarbonyl)-*N*-methylpiperazine-1-sulfonamide (TFA salt, 45 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (m, 2H), 0.95 (m, 2H), 1.53 (m, 4H), 1.57 (s, 9H), 1.69 (m, 1H), 2.32 (m, 1H), 3.21 (m, 2H), 3.28 (m, 2H), 3.30 (s, 3H), 3.33 (m, 2H), 3.60 (m, 2H), 3.70 (m, 2H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 518.0.

Example 79

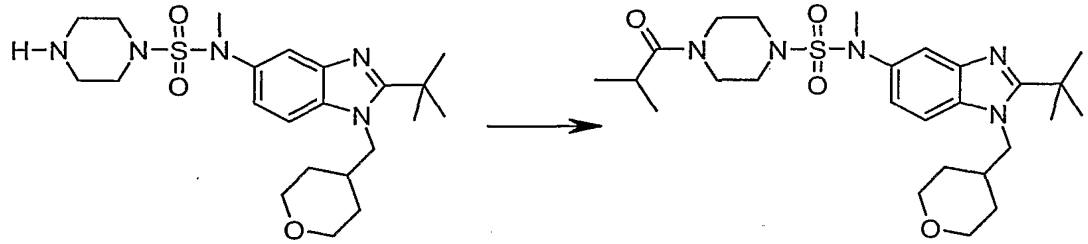
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-propionylpiperazine-1-sulfonamide



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (60 mg, 0.13 mmol) was reacted with propanoic anhydride (26 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-propionylpiperazine-1-sulfonamide (TFA salt, 28 mg, 35 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J=7.4 Hz, 3H), 1.53 (m, 4H), 1.57 (s, 9H), 2.32 (m, 3H), 3.14 (m, 2H), 3.25 (m, 2H), 3.30 (s, 3H), 3.33 (m, 2H), 3.45 (m, 2H), 3.60 (m, 2H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 506.0.

Example 80

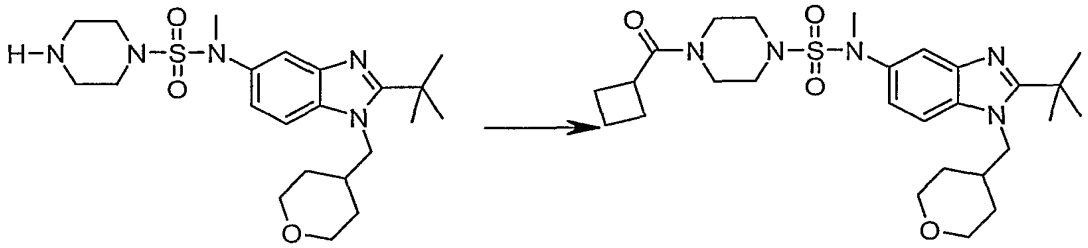
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-isobutyryl-*N*-methylpiperazine-1-sulfonamide**



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with 2-methylpropanoyl chloride (22 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-isobutyryl-*N*-methylpiperazine-1-sulfonamide (TFA salt, 35 mg, 50 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (d, J=6.6 Hz, 6H), 1.53 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 2.73 (m, 1H), 3.15 (m, 2H), 3.30 (m, 2H), 3.31 (s, 3H), 3.33 (m, 2H), 3.50 (m, 2H), 3.60 (m, 2H), 3.99 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 520.0.

Example 81

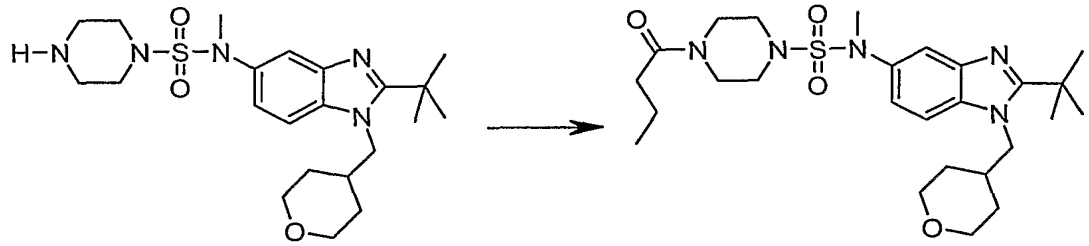
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclobutylcarbonyl)-*N*-methylpiperazine-1-sulfonamide**



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with cyclobutanecarbonyl chloride (24 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclobutylcarbonyl)-*N*-methylpiperazine-1-sulfonamide (TFA salt, 34 mg, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (m, 4H), 1.57 (s, 9H), 1.80 -2.00 (m, 2H), 2.13 (m, 2H), 2.31 (m, 3H), 3.14 (m, 2H), 3.20 (m, 3H), 3.30 (s, 3H), 3.32 (m, 4H), 3.35 (m, 2H), 3.91 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 532.0.

Example 82

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-butyryl-*N*-methylpiperazine-1-sulfonamide**

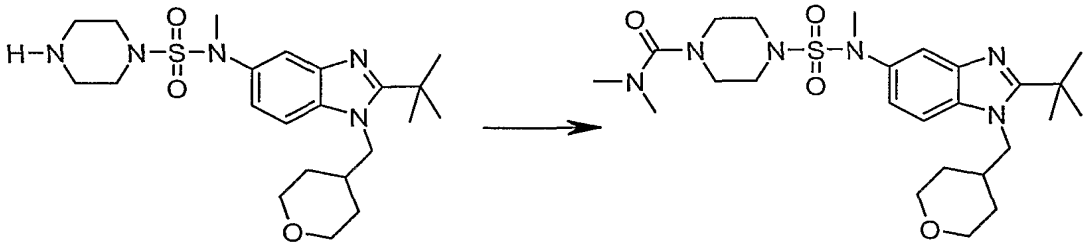


Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with butanoyl chloride (21 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-butyryl-*N*-methylpiperazine-1-sulfonamide (TFA

salt, 28 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J=7.4 Hz, 3H), 1.53 (m, 4H), 1.57 (s, 9H), 1.65 (m, 2H), 2.27 (t, J=7.4 Hz, 2H), 2.30 (m, 1H), 3.14 (m, 2H), 3.24 (m, 2H), 3.30 (s, 3H), 3.33 (m, 2H), 3.45 (m, 2H), 3.60 (m, 2H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.32 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 520.0.

Example 83

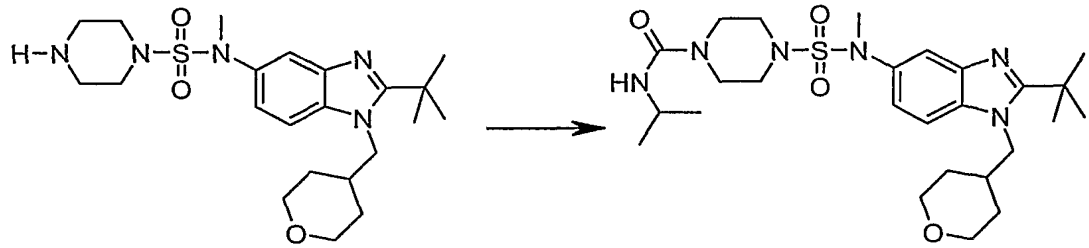
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperazine-1-carboxamide



Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (45 mg, 0.1 mmol) was reacted with dimethylcarbamoyl chloride (22 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperazine-1-carboxamide (TFA salt, 56 mg, 88 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.54 (m, 4H), 1.67 (s, 9H), 2.37 (m, 1H), 2.82 (s, 6H), 3.23 (m, 6H), 3.33 (s, 3H), 3.36 (m, 4H), 3.91 (m, 2H), 4.53 (d, J = 7.6 Hz, 2H), 7.68 (d, J=9.2 Hz, 1H), 7.81 (s, 1H), 7.96 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$ 521.0.

Example 84

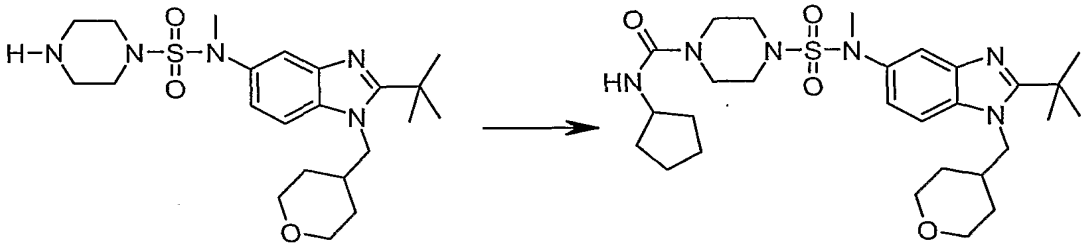
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (45 mg, 0.1 mmol) was reacted with isopropyl isocyanate (17 mg, 0.2 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide (TFA salt, 64 mg, 98 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.10 (d, J=6.4 Hz, 6H), 1.58 (m, 4H), 1.67 (s, 9H), 2.35 (m, 1H), 3.20 (m, 4H), 3.33 (s, 3H), 3.37 (m, 6H), 3.85 (m, 1H), 3.91 (m, 2H), 4.53 (d, J = 7.6 Hz, 2H), 7.67 (d, J=9.2 Hz, 1H), 7.81 (s, 1H), 7.96 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$ 535.0.

Example 85

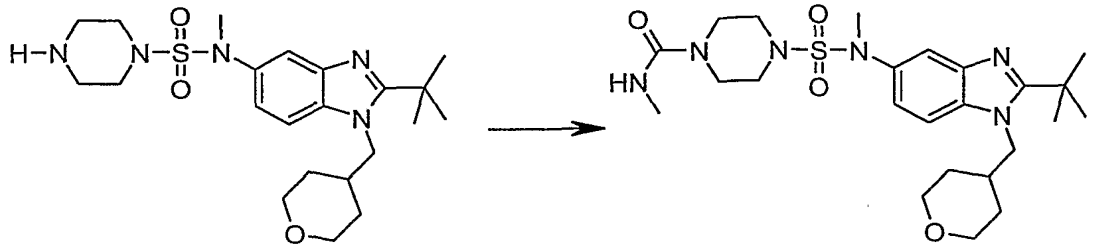
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (90 mg, 0.2 mmol) was reacted with isocyanatocyclopentane (44 mg, 0.4 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperazine-1-carboxamide (TFA salt, 135 mg, 100 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 2H), 1.54 (m, 4H), 1.57 (s, 9H), 1.59 (m, 4H), 1.97 (m, 2H), 2.30 (m, 1H), 3.19 (m, 4H), 3.30 (s, 3H), 3.33 (m, 6H), 4.02 (m, 2H), 4.07 (m, 1H), 4.20 (d, J = 7.6 Hz, 2H), 4.38 (m, 1H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 561.0.

Example 86

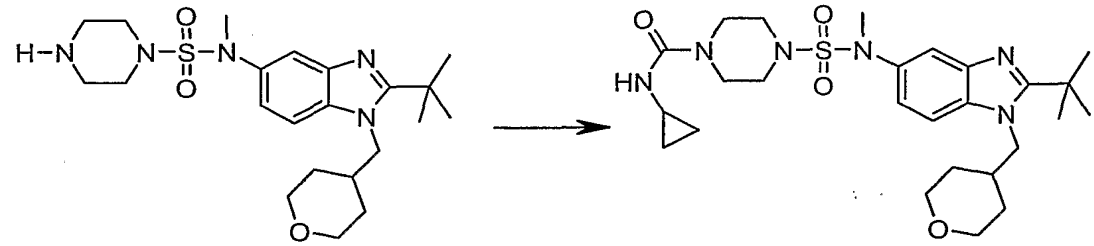
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (60 mg, 0.13 mmol) was reacted with methyl isocyanate (17 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide (TFA salt, 75 mg, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.48 (s, 9H), 2.21 (m, 1H), 2.68 (m, 3H), 3.10 (m, 4H), 3.21 (s, 3H), 3.28 (m, 6H), 3.91 (m, 2H), 4.12 (d, J = 7.6 Hz, 2H), 4.78 (m, 1H), 7.23 (m, 2H), 7.62 (s, 1H); MS (ESI) $(M+H)^+$ 507.0.

Example 87

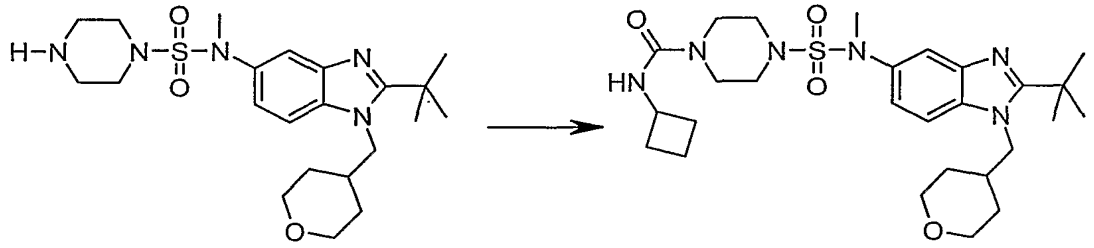
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with cyclopropyl isocyanate (25 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide (TFA salt, 56 mg, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (m, 2H), 0.68 (m, 2H), 1.53 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 2.61 (m, 1H), 3.18 (m, 4H), 3.30 (s, 3H), 3.33 (m, 6H), 3.99 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 5.01 (s, 1H), 7.31 (m, 2H), 7.70 (s, 1H); MS (ESI) $(M+H)^+$ 533.0.

Example 88

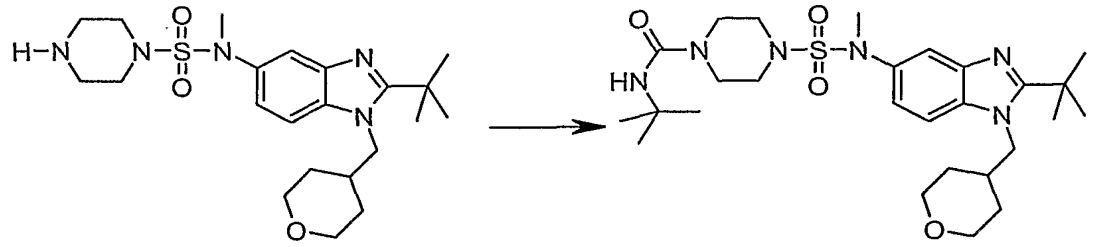
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with cyclobutyl isocyanate (29 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide (TFA salt, 39 mg, 54 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (m, 4H), 1.57 (s, 9H), 1.69 (m, 2H), 1.79 (m, 2H), 2.30 (m, 3H), 3.19 (m, 4H), 3.30 (s, 3H), 3.34 (m, 6H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 4.23 (m, 1H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 547.0.

Example 89

***N*-(*tert*-Butyl)-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide**

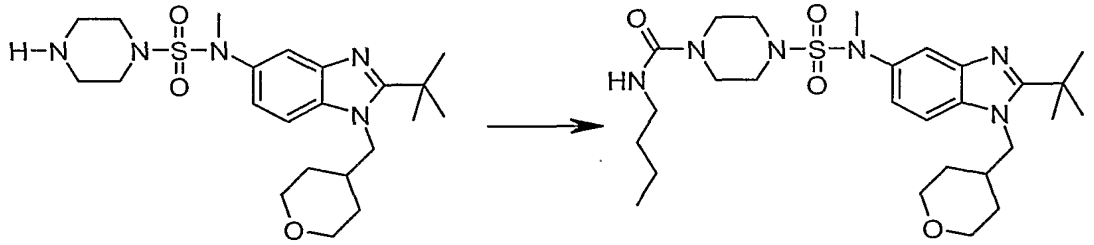


Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with *tert*-butyl isocyanate (29 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide *N*-(*tert*-butyl)-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-

yl](methyl)amino]sulfonyl}piperazine-1-carboxamide (TFA salt, 29 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.53 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 3.20 (m, 4H), 3.30 (s, 3H), 3.33 (m, 6H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 549.0.

Example 90

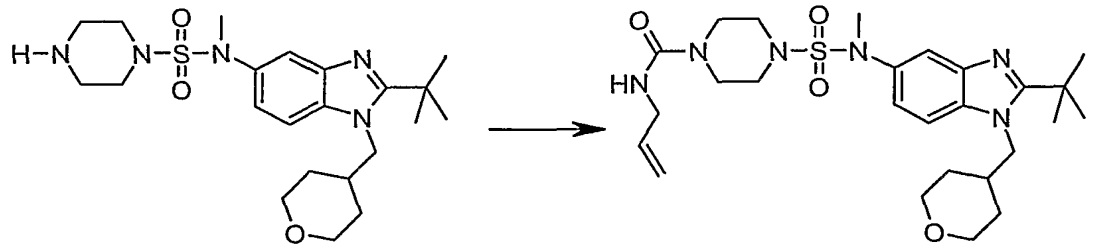
***N*-Butyl-4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide**



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with butyl isocyanate (29 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide *N*-butyl-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide (TFA salt, 26 mg, 36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J=7.2 Hz, 3H), 1.33 (m, 2H), 1.46 (m, 2H), 1.53 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 3.16 (m, 6H), 3.30 (s, 3H), 3.35 (m, 4H), 3.99 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 549.0.

Example 91

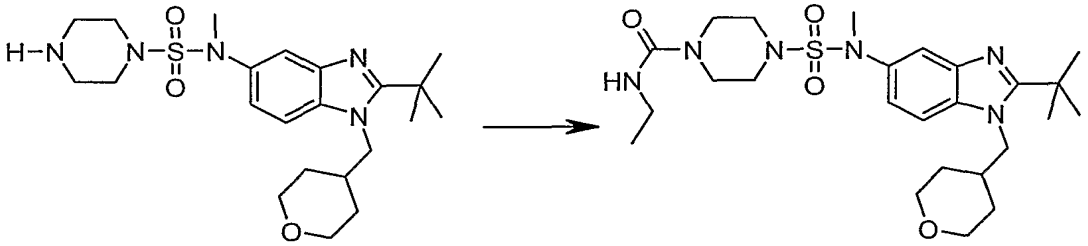
***N*-Allyl-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide**



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with 3-isocyanatoprop-1-ene (25 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide *N*-allyl-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide (TFA salt, 29 mg, 41 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 3.21 (m, 4H), 3.30 (s, 3H), 3.37 (m, 6H), 3.84 (m, 2H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 5.11 (m, 1H), 5.17 (m, 1H), 5.85 (m, 1H), 7.31 (m, 2H), 7.73 (s, 1H); MS (ESI) $(M+H)^+$ 533.0.

Example 92

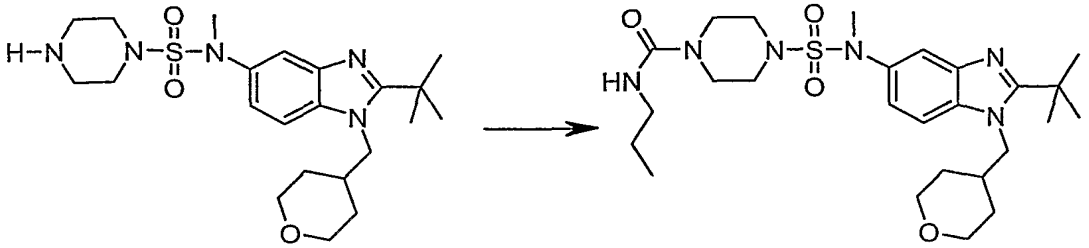
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with isocyanatoethane (21 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperazine-1-carboxamide (TFA salt, 13 mg, 19 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J=7.2 Hz, 3H), 1.53 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 3.20 (m, 6H), 3.30 (s, 3H), 3.33 (m, 4H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 521.0.

Example 93

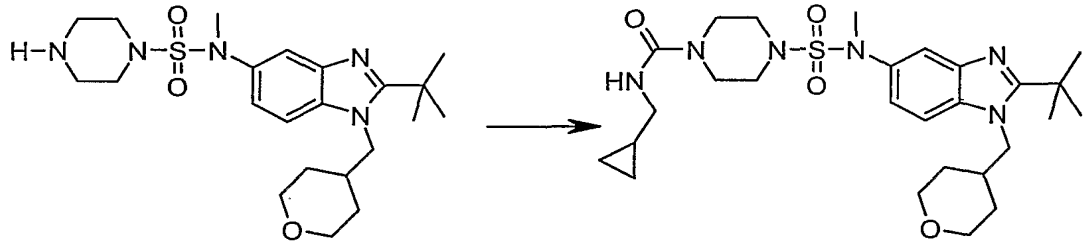
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with 1-isocyanatopropane (25 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperazine-1-carboxamide (TFA salt, 24 mg, 34 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J=7.6 Hz, 3H), 1.53 (m, 6H), 1.57 (s, 9H), 2.33 (m, 1H), 3.20 (m, 6H), 3.30 (s, 3H), 3.33 (m, 4H), 3.98 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 535.0.

Example 94

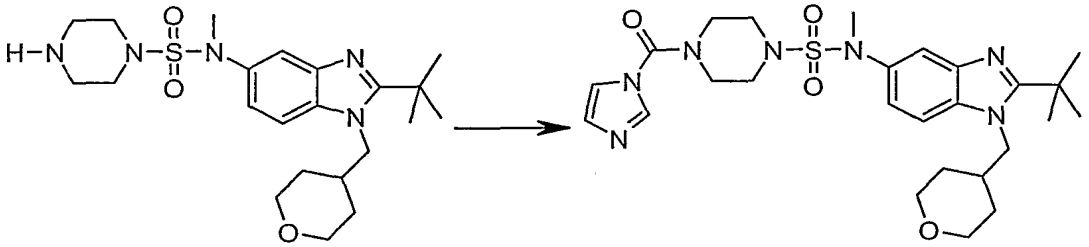
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(cyclopropylmethyl)piperazine-1-carboxamide



Following the procedure in Step A of Example 68, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (50 mg, 0.11 mmol) was reacted with (isocyanatomethyl)cyclopropane (28 mg, 0.3 mmol), after being purified by reverse phase HPLC, to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(cyclopropylmethyl)piperazine-1-carboxamide (TFA salt, 35 mg, 48 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.17 (m, 2H), 0.50 (m, 2H), 0.94 (m, 1H), 1.54 (m, 4H), 1.57 (s, 9H), 2.30 (m, 1H), 3.06 (m, 2H), 3.20 (m, 4H), 3.30 (s, 3H), 3.37 (m, 6H), 3.99 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 7.31 (m, 2H), 7.72 (s, 1H); MS (ESI) $(M+H)^+$ 547.0.

Example 95

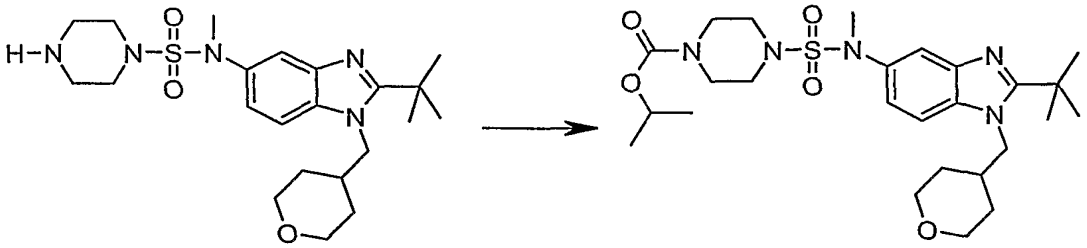
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(1*H*-imidazol-1-ylcarbonyl)-*N*-methylpiperazine-1-sulfonamide**



A solution of *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (2.25 g, 5.0 mmol) and 1,1'-biscarbonyl-1*H*-imidazole (0.97 g, 6.0 mmol) in THF (40 mL) was heated at 65^{0}C for two days. The reaction mixture was concentrated under reduced pressure. The residue was then dissolved in AcOEt (60 mL), washed with brine, and dried over Na_2SO_4. Removal of solvents provided *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(1*H*-imidazol-1-ylcarbonyl)-*N*-methylpiperazine-1-sulfonamide (2.6 g, 96 %), ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.54 (m, 4H), 1.68 (s, 9H), 2.37 (m, 1H), 3.32 (m, 2H), 3.34 (s, 3H), 3.42 (m, 4H), 3.65 (m, 4H), 3.92 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 7.67 (m, 2H), 7.84 (s, 1H), 7.90 (s, 1H), 7.97 (d, J=8.8 Hz, 1H), 9.32 (s, 1H); MS (ESI) $(M+H)^+$ 543.8.

Example 96

Isopropyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate

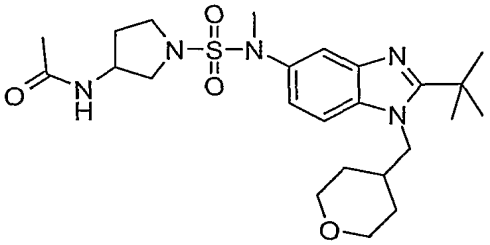


Following the procedure in Step A of Example 60, *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide (45 mg, 0.10 mmol) was reacted with isopropyl chloroformate (25 mg, 0.2 mmol), after

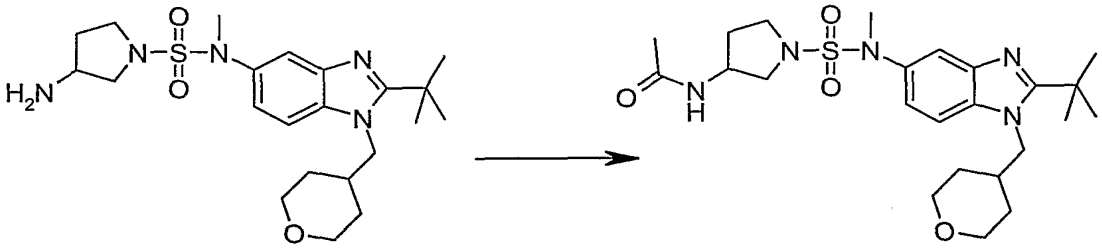
being purified by reverse phase HPLC, to isopropyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate (TFA salt, 62 mg, 94 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J=6.3 Hz, 6H), 1.47 (m, 4H), 1.49 (s, 9H), 2.22 (m, 1H), 3.10 (m, 4H), 3.23 (s, 3H), 3.23 (m, 2H), 3.37 (m, 4H), 3.91 (m, 2H), 4.13 (d, J = 7.6 Hz, 2H), 4.83 (m, 1H), 7.23 (m, 2H), 7.64 (s, 1H); MS (ESI) $(M+H)^+$ 536.0.

Example 97

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)acetamide**

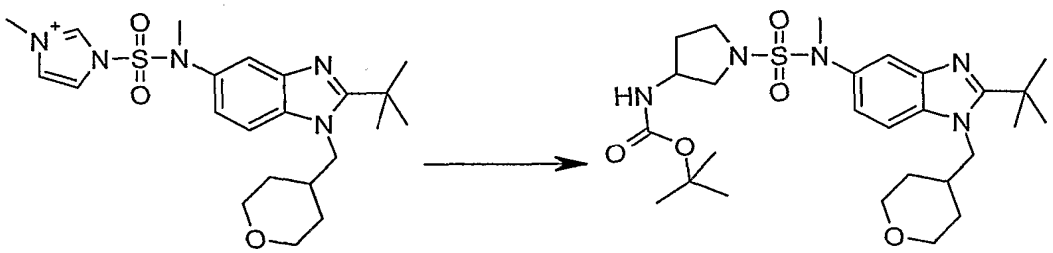


Step A. *N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)acetamide



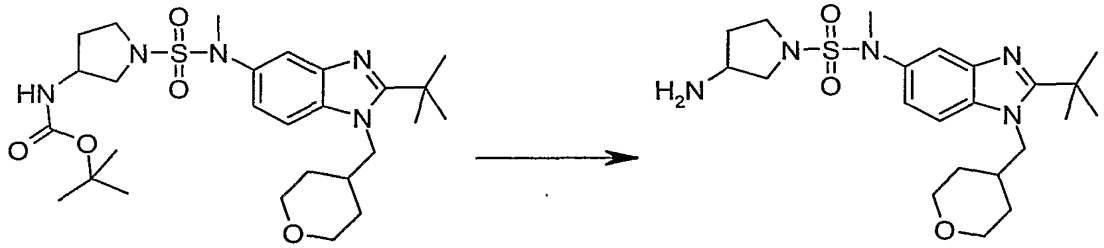
Following the procedure in Step A of Example 60, 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide trifluoroacetate (100 mg, 0.18 mmol) was reacted with acetyl chloride (79 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide *N*-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)acetamide (TFA salt, 25 mg, 23 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.54 (m, 4H), 1.67 (s, 9H), 1.85 (m, 1H), 1.89 (s, 3H), 2.13 (m, 1H), 2.36 (m, 1H), 3.10 (m, 1H), 3.31 (s, 3H), 3.33 (m, 3H), 3.48 (m, 2H), 3.91 (m, 2H), 4.20 (m, 1H), 4.52 (d, J = 7.6 Hz, 2H), 7.65 (d, J=9.0 Hz, 1H), 7.79 (s, 1H), 7.93 (d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 492.0.

Step B. *tert*-Butyl (1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)carbamate



Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (460 mg, 0.77 mmol) was reacted with *tert*-butyl pyrrolidin-3-ylcarbamate (558 mg, 3.0 mmol), after being purified by silica gel chromatography, to provide *tert*-butyl (1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)carbamate (385 mg, 91 %). MS (ESI) $(M+H)^+$ 550.0.

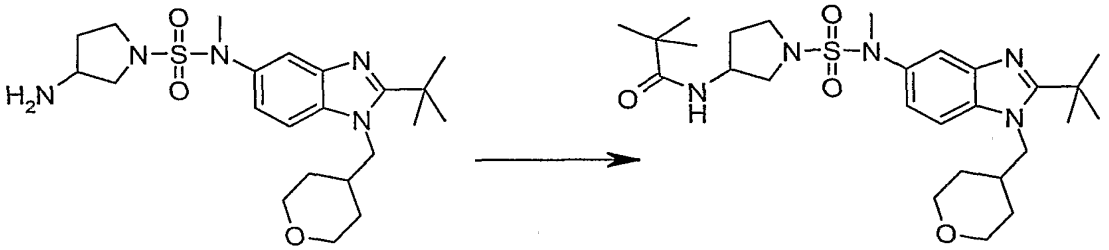
Step C: 3-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide



A solution of *tert*-butyl (1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)carbamate (385 mg, 0.7 mmol) in 10 mL CH_2Cl_2 was treated with 10 mL TFA at room temperature. After being stirred at room temperature for 1 hr, the reaction mixture was concentrated under reduced pressure to provide 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide (TFA salt, 100 %), which was used in Step A without purification.

Example 98

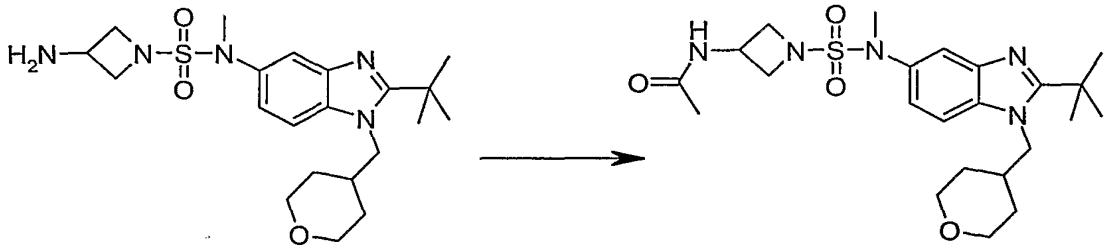
***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)-2,2-dimethylpropanamide**



Following the procedure in Step A of Example 60, 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide trifluoroacetate (100 mg, 0.18 mmol) was reacted with 2,2-dimethylpropanoyl chloride (60 mg, 0.5 mmol), after being purified by reverse phase HPLC, to provide *N*-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)-2,2-dimethylpropanamide (TFA salt, 39 mg, 33 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.12 (s, 9H), 1.57 (m, 4H), 1.67 (s, 9H), 1.96 (m, 1H), 2.11 (m, 1H), 2.36 (m, 1H), 3.10 (m, 1H), 3.31 (s, 3H), 3.33 (m, 3H), 3.48 (m, 2H), 3.91 (m, 2H), 3.94 (m, 1H), 4.52 (d, J = 7.6 Hz, 2H), 7.65 (d, J=9.0 Hz, 1H), 7.79 (s, 1H), 7.94 (d, J=9.0 Hz, 1H); MS (ESI) $(M+H)^+$ 534.0.

Example 99

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)acetamide**

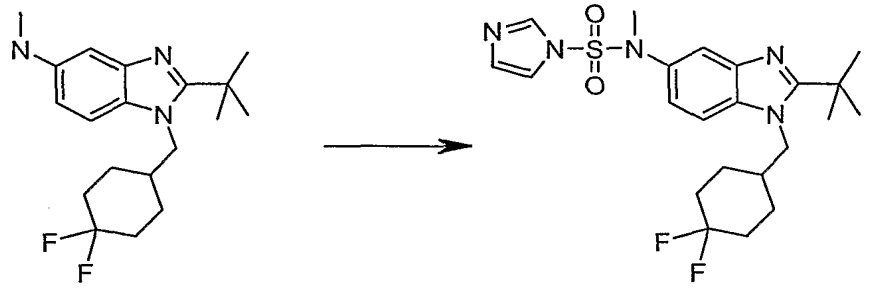


Following the procedure in Step A of Example 60, 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylazetidine-1-sulfonamide (20 mg, 0.046 mmol) was reacted with acetic anhydride (51 mg, 0.5 mmol), after being purified by reverse phase HPLC, to provide *N*-(1-{[[2-*tert*-butyl-

1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)acetamide (TFA salt, 9 mg, 33 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.58 (m, 4H), 1.67 (s, 9H), 1.91 (s, 3H), 2.32 (m, 1H), 3.28 (s, 3H), 3.33 (m, 2H), 3.80 (m, 2H), 3.91 (m, 2H), 3.99 (m, 2H), 4.50 (m, 1H), 4.53 (d, J = 7.6 Hz, 2H), 7.65 (d, J=9.2 Hz, 1H), 7.78 (s, 1H), 7.95 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$ 478.0.

Example 100

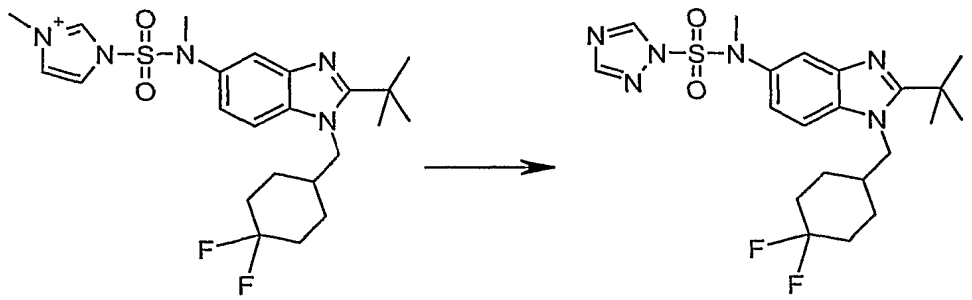
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide**



3-(Imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium triflate (xx mg; 1.5 mmol) was added into a solution of 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (335 mg, 1.0 mmol) in acetonitrile (15 mL). After being stirred at room temperature overnight, the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by HPLC to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide (295 mg, 51 %). MS (ESI) $(M+H)^+$ 466.0.

Example 101

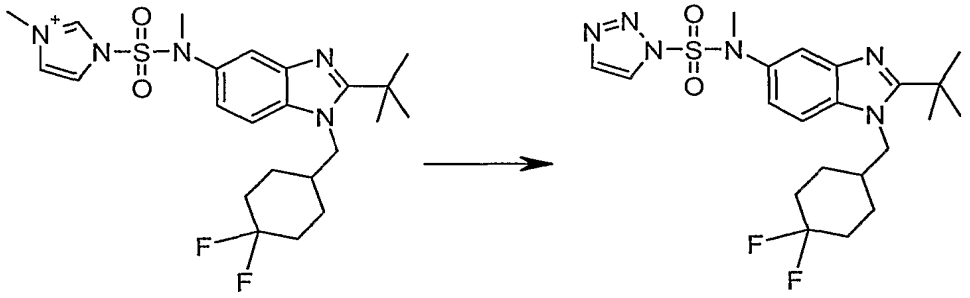
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,4-triazole-1-sulfonamide**



Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (50 mg, 0.08 mmol) was reacted with 1*H*-1,2,4-triazole (69 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,4-triazole-1-sulfonamide (TFA salt, 15 mg, 32 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.62 (s, 9H), 2.03 (m, 2H), 2.20 (m, 1H), 3.55 (s, 3H), 4.48(d, J = 7.4 Hz, 2H), 7.36(d, J=9.0 Hz, 1H), 7.60 (s, 1H), 7.86(d, J=9.0 Hz, 1H), 8.28 (s, 1H), 8.72(s, 1H); MS (ESI) $(M+H)^+$ 467.0.

Example 102

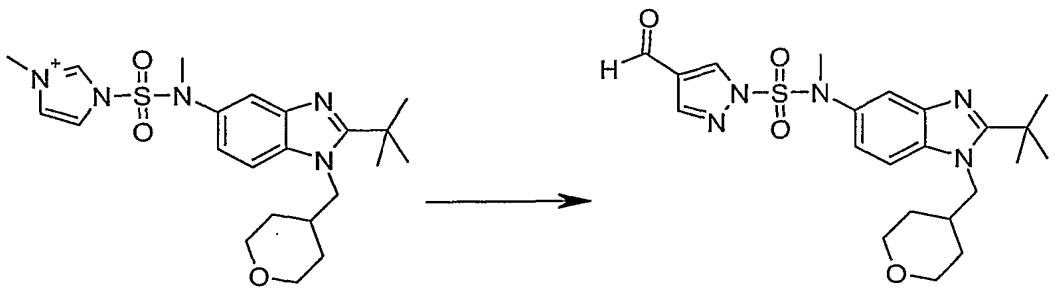
***N*-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,3-triazole-1-sulfonamide**



Following the procedure in Step C of Example 60, 1-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (50 mg, 0.08 mmol) was reacted with 1*H*-1,2,3-triazole (69 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,3-triazole-1-sulfonamide (TFA salt, 14 mg, 30 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.40-1.76 (m, 6H), 1.59 (s, 9H), 2.03 (m, 2H), 2.20 (m, 1H), 3.56 (s, 3H), 4.42 (d, J = 7.4 Hz, 2H), 7.22(d, J=9.0 Hz, 1H), 7.47 (s, 1H), 7.75(d, J=9.0 Hz, 1H), 7.82 (d, J=1.1 Hz, 1H), 8.21 (d, J=1.1 Hz, 1H); MS (ESI) $(M+H)^+$ 467.0.

Example 103

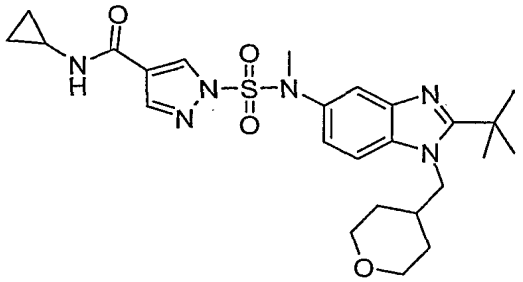
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide**



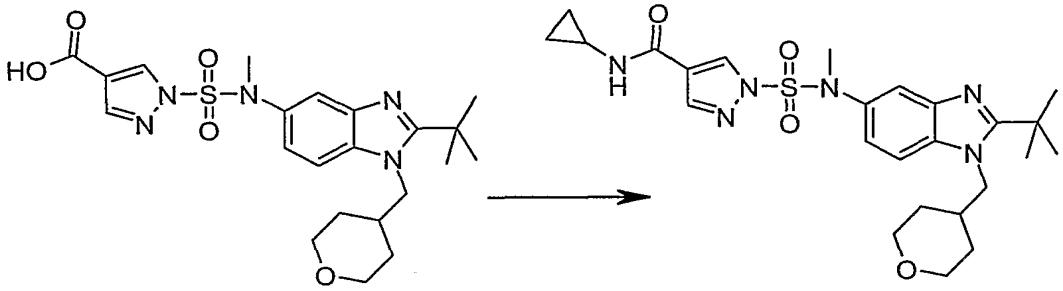
Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (1.89 g, 3.0 mmol) was reacted with 1*H*-pyrazole-4-carbaldehyde (576 mg, 6.0 mmol), after being purified by silica gel chromatography, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide (586 mg, 43 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (m, 4H), 1.50 (s, 9H), 2.22 (m, 1H), 3.27 (m, 2H), 3.55 (s, 3H), 3.91 (m, 2H), 4.14 (d, J = 7.2 Hz, 2H), 6.98 (dd, J = 8.8, 2.0 Hz, 1H), 7.925 (d, J = 8.8 Hz, 1H), 7.37 (s, 1H), 8.14 (s, 1H), 8.18 (s, 1H), 9.81 (s, 1H); MS (ESI) $(M+H)^+$ 460.0.

Example 104

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-4-carboxamide

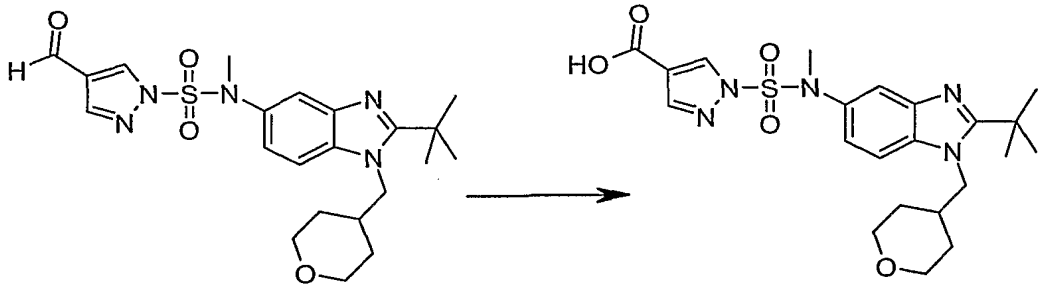


Step A. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-4-carboxamide



HATU (150 mg, 0.4 mmol) was added to a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (100 mg, 0.21 mmol), cyclopropylamine (57 mg, 1.0 mmol) and DIPEA (0.2 mL) in DMF (3.0 mL) at r.t. After 30 min, the reaction mixture was condensed to give a residue, which was purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-4-carboxamide (TFA salt, 29 mg, 22 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (m, 2H), 0.80 (m, 2H), 1.54 (m, 4H), 1.56 (s, 9H), 2.33 (m, 1H), 2.82 (m, 1H), 3.33 (m, 2H), 3.55 (s, 3H), 3.99 (m, 2H), 4.20 (d, J = 7.6 Hz, 2H), 6.40 (s, 1H), 7.06 (dd, J = 9.0, 2.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.38 (s, 1H), 8.02 (s, 1H), 8.05 (d, J=3.5 Hz, 1H); MS (ESI) $(M+H)^+$515.0.

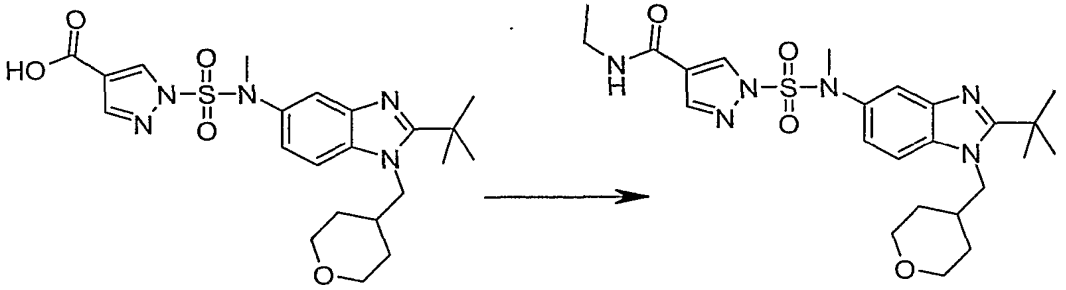
Step B. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid



N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide (460 mg, 1.0 mmol) and ozone (1.0 g, 1.6 mmol) was heated in DMF (15 mL) at 50 ^{0}C for 2 hr. The resulting 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid solution in DMF was used directly in Step A. MS (ESI) $(M+H)^+$ 476.0.

Example 105

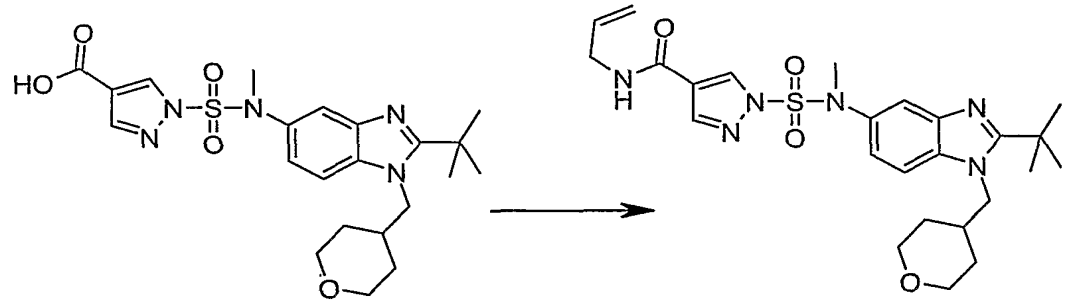
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-4-carboxamide



Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with ethylamine (90 mg, 2.0 mmol), after being purified by reverse phase HPLC, to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-4-carboxamide (TFA salt, 33 mg, 27 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.14 (d, J = 7.4 Hz, 3H), 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 3.32 (m, 4H), 3.51 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 7.42 (dd, J = 9.0, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.18 (s, 1H), 8.30 (s, 1H); MS (ESI) $(M+H)^+$502.8.

Example 106

***N*-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide**

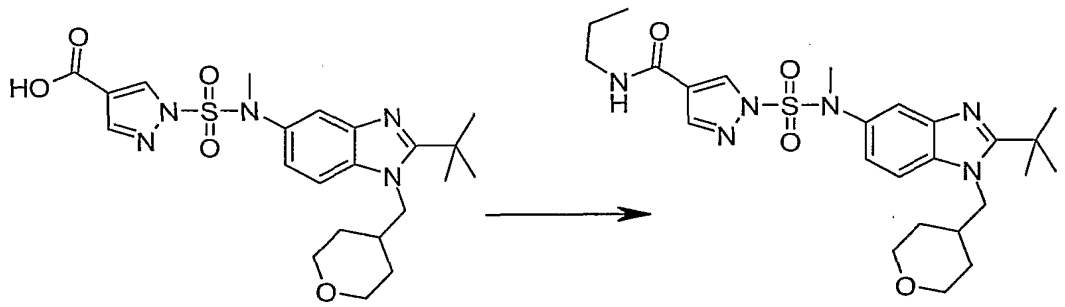


Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with allylamine (114 mg, 2.0

mmol), after being purified by reverse phase HPLC, to provide *N*-allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide (TFA salt, 38 mg, 30 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 3.32 (m, 4H), 3.52 (s, 3H), 3.91 (m, 4H), 4.51 (d, J = 7.6 Hz, 2H), 5.09 (m, 1H), 5.17 (m, 1H), 5.85 (m, 1H), 7.42 (dd, J = 9.0, 2.0 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.20 (s, 1H), 8.32 (s, 1H); MS (ESI) $(M+H)^+$515.0.

Example 107

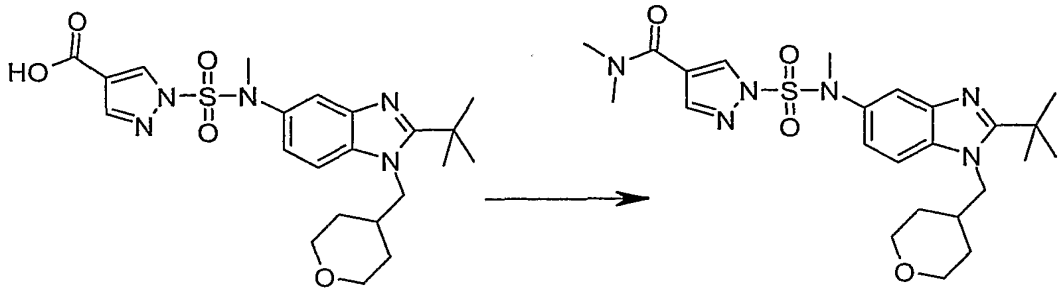
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-4-carboxamide



Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with propylamine (118 mg, 2.0 mmol), after being purified by reverse phase HPLC, to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-4-carboxamide (TFA salt, 44 mg, 35 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 0.91 (d, J = 7.4 Hz, 3H), 1.52 (m, 6H), 1.65 (s, 9H), 2.33 (m, 1H), 3.23 (t, J=7.2 Hz, 2H), 3.32 (m, 2H), 3.52 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 7.41 (dd, J = 9.0, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.19 (s, 1H), 8.31 (s, 1H); MS (ESI) $(M+H)^+$516.8.

Example 108

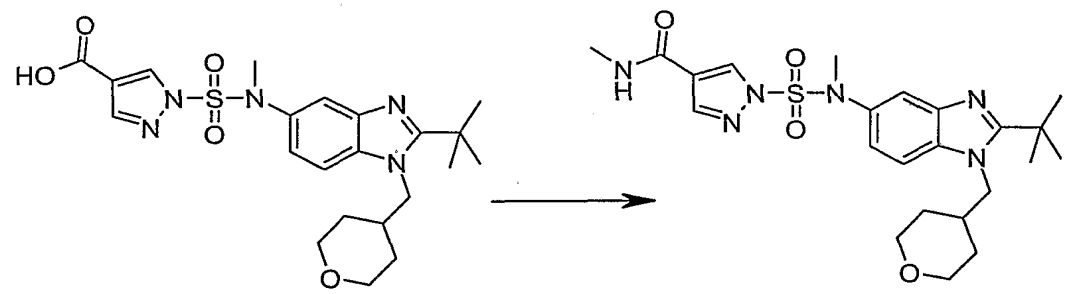
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide



Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with dimethylamine (90 mg, 2.0 mmol), after being purified by reverse phase HPLC, to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide (TFA salt, 79 mg, 64 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.53 (m, 4H), 1.66 (s, 9H), 2.33 (m, 1H), 3.02 (s, 3H), 3.12 (s, 3H), 3.32 (m, 2H), 3.51 (s, 3H), 3.89 (m, 2H), 4.52 (d, J = 7.6 Hz, 2H), 7.41 (dd, J = 9.0, 2.0 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.09 (s, 1H), 8.16 (s, 1H); MS (ESI) $(M+H)^+$502.8.

Example 109

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methyl-1*H*-pyrazole-4-carboxamide

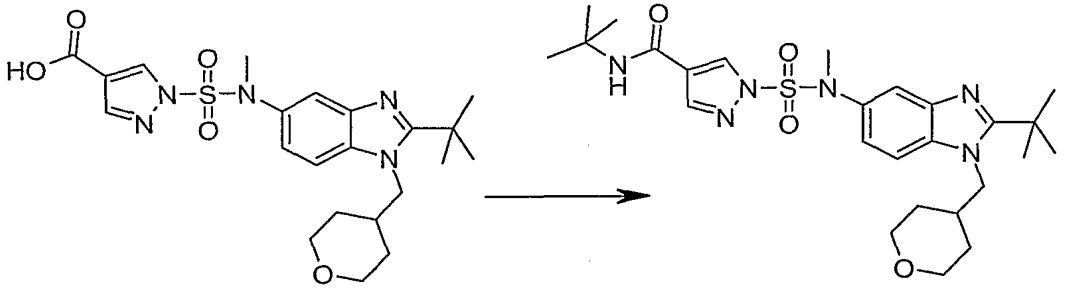


Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with methylamine (31 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methyl-1*H*-pyrazole-4-carboxamide (TFA salt, 24 mg, 20 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 2.81 (s, 3H), 3.32 (m,

2H), 3.52 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 7.41 (dd, J = 9.0, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.17 (s, 1H), 8.27 (s, 1H); MS (ESI) $(M+H)^+$488.7.

Example 110

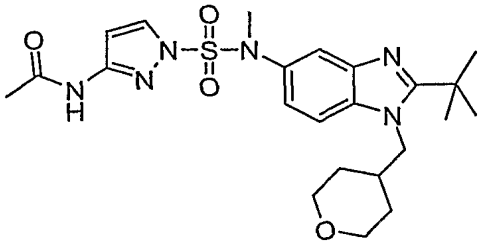
***N*-(*tert*-Butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide**



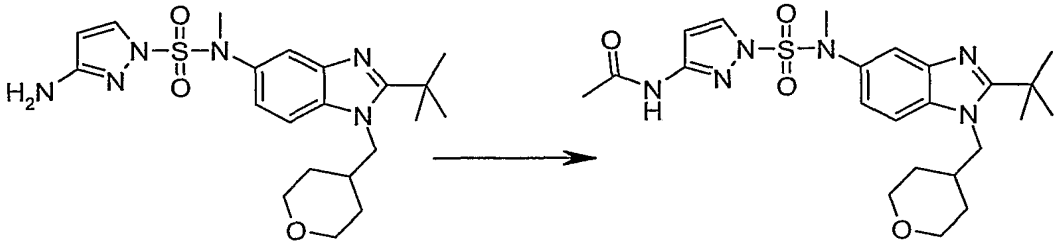
Following the procedure in Step A of Example 104, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxylic acid (96 mg, 0.20 mmol) was reacted with t-butylamine (73 mg, 1.0 mmol), after being purified by reverse phase HPLC, to provide *N*-(*tert*-butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide (TFA salt, 26 mg, 20 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.37 (s, 9H), 1.52 (m, 4H), 1.66 (s, 9H), 2.33 (m, 1H), 3.32 (m, 2H), 3.51 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 7.44 (dd, J = 9.0, 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.17 (s, 1H), 8.36 (s, 1H); MS (ESI) $(M+H)^+$530.8.

Example 111

***N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazol-3-yl)acetamide**

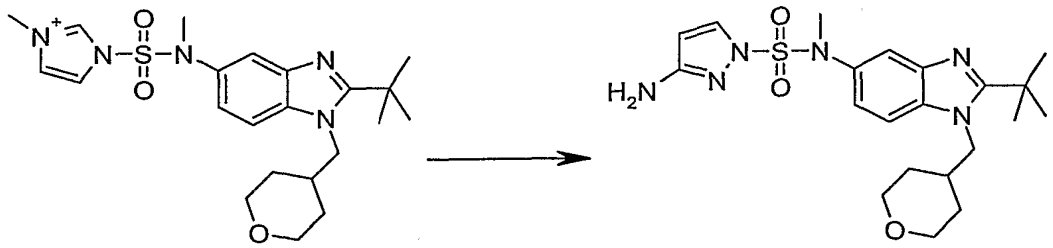


Step A. *N*-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazol-3-yl)acetamide



Following the procedure in Step A of Example 60, 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-1*H*-pyrazole-1-sulfonamide (from Step B) was reacted with acetic anhydride (530 mg, 5.0 mmol), after being purified by silica gel chromatography, to provide *N*-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazol-3-yl)acetamide (3 mg, 2 %). ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 1.52 (m, 4H), 1.66 (s, 9H), 2.14 (s, 3H), 2.34 (m, 1H), 3.32 (m, 2H), 3.51 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 6.75 (d, J = 2.8 Hz, 1H), 7.41 (dd, J = 9.0, 2.2 Hz, 1H), 7.54 (s, 1H), 7.68 (d, J = 2.8 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$489.0.

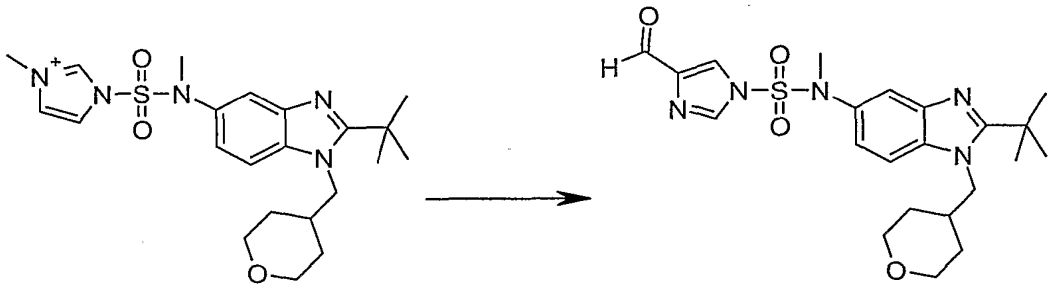
Step B. 3-Amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-1*H*-pyrazole-1-sulfonamide



Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (189 mg, 0.3 mmol) was reacted with 1*H*-pyrazol-3-amine (83 mg, 1.0 mmol), after being purified by silica gel chromatography, to provide crude 3-amino-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-1*H*-pyrazole-1-sulfonamide, which was used in Step A without further purification.

Example 112

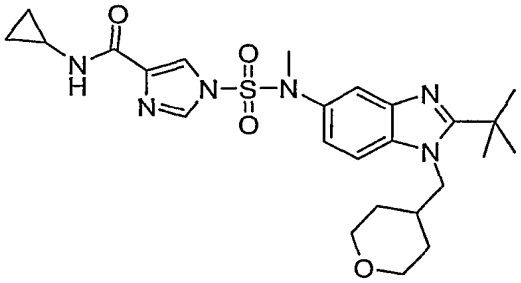
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-imidazole-1-sulfonamide**



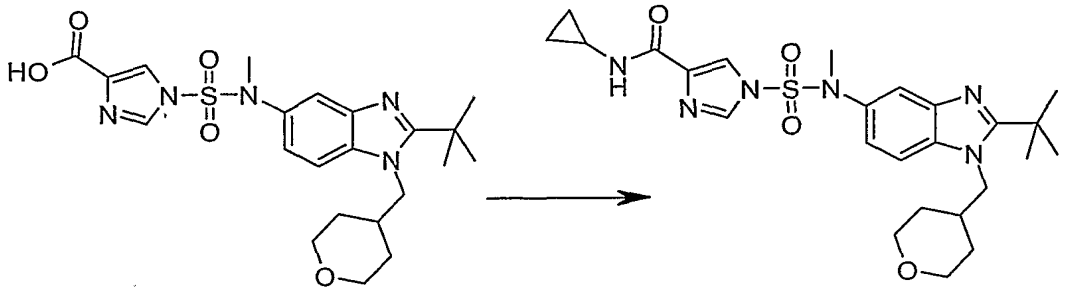
Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (630 g, 1.0 mmol) was reacted with 1*H*-imidazole-4-carbaldehyde (288 mg, 3.0 mmol), after being purified by silica gel chromatography, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-imidazole-1-sulfonamide (335 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (m, 4H), 1.54 (s, 9H), 2.25 (m, 1H), 3.32 (m, 2H), 3.60 (s, 3H), 3.98 (m, 2H), 4.19 (d, J = 7.6 Hz, 2H), 6.81 (s, 1H), 7.01 (dd, J = 8.6, 1.9 Hz, 1H), 7.32 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.74 (s, 1H), 10.12 (s, 1H); MS (ESI) $(M+H)^+$ 460.0.

Example 113

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-imidazole-4-carboxamide

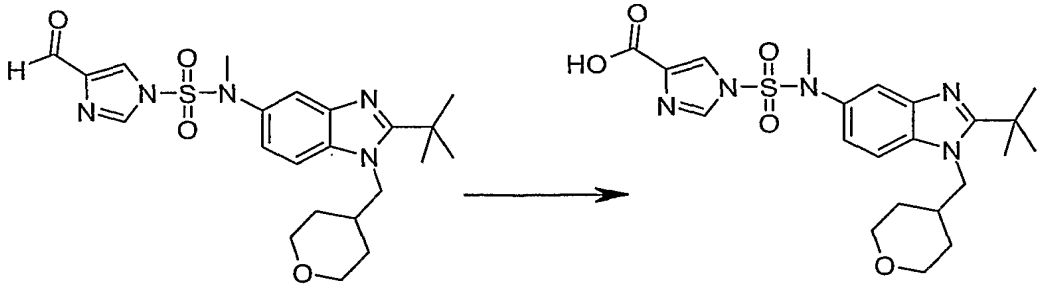


Step A. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-imidazole-4-carboxamide



HATU (15 mg, 0.04 mmol) was added to a solution of 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-imidazole-4-carboxylic acid (10 mg, 0.02 mmol), cyclopropylamine (6 mg, 0.1 mmol) and DIPEA (0.1 mL) in DMF (1.0 mL) at r.t. After 30 min, the reaction mixture was condensed to give a residue, which was purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-imidazole-4-carboxamide (TFA salt, 2 mg, 15 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.61 (m, 2H), 0.80 (m, 2H), 1.54 (m, 4H), 1.68 (s, 9H), 2.35 (m, 1H), 2.80 (m, 1H), 3.33 (m, 2H), 3.46 (s, 3H), 3.93 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 7.37 (dd, J = 9.0, 1.9 Hz, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.72 (s, 1H), 7.91 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$514.8.

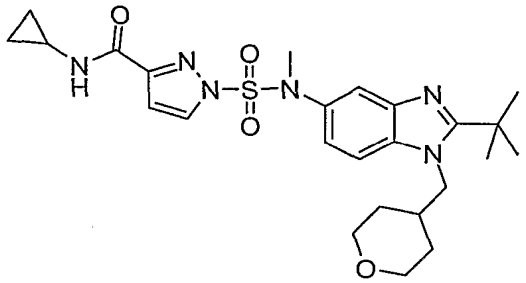
Step B. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-imidazole-4-carboxylic acid



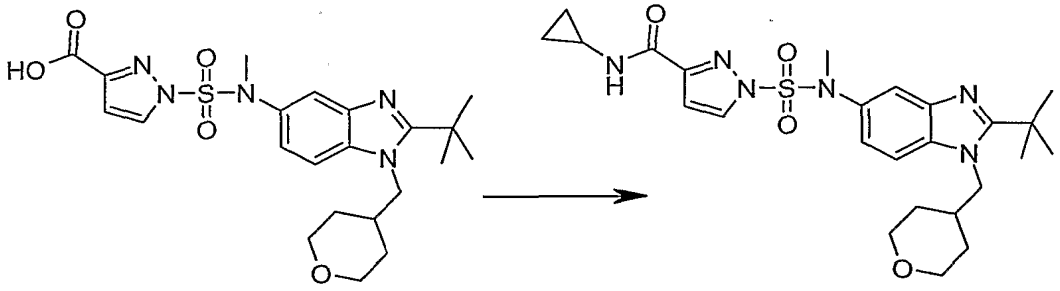
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-imidazole-1-sulfonamide (320 mg, 0.7 mmol) and ozone (650 mg, 1.1 mmol) was heated in DMF (6 mL) at r.t for 24 hr. The resulting 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-imidazole-4-carboxylic acid solution in DMF was used directly in Step A. MS (ESI) $(M+H)^+$ 476.0.

Example 114

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-3-carboxamide

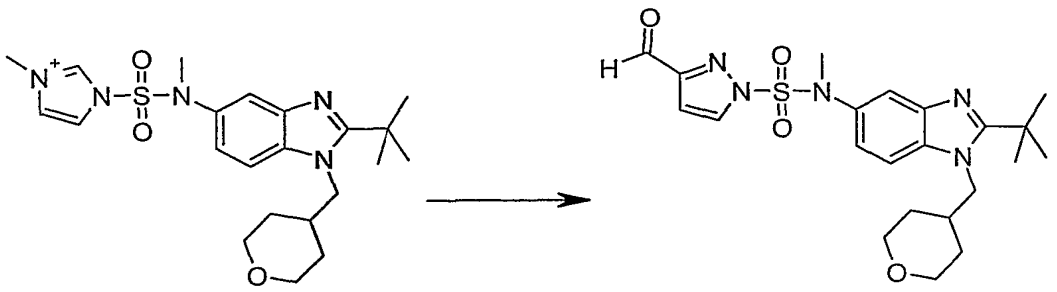


Step A. 1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-3-carboxamide



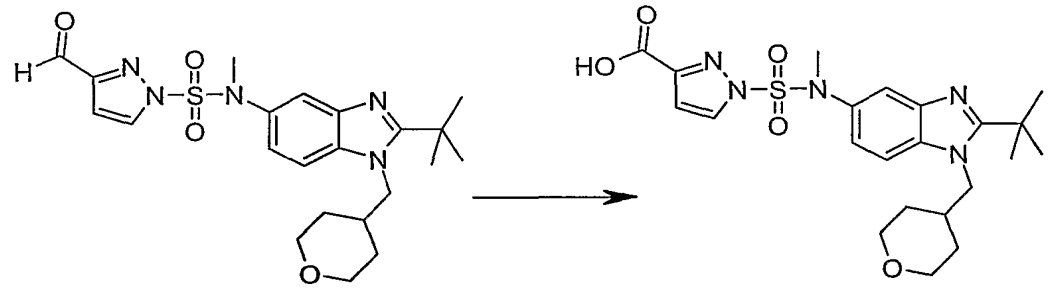
HATU (250 mg, 0.66 mmol) was added to a solution of 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid (65 mg, 0.14 mmol), cyclopropylamine (57 mg, 1.0 mmol) and DIPEA (0.4 mL) in DMF (1.0 mL) at r.t. After 30 min, the reaction mixture was condensed to give a residue, which was purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-3-carboxamide (TFA salt, 19 mg, 22 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (m, 2H), 0.81 (m, 2H), 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 2.84 (m, 1H), 3.33 (m, 2H), 3.56 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 2.8 Hz, 1H), 7.39 (dd, J = 9.0, 2.0 Hz, 1H), 7.52 (s, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$514.8.

Step B. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-3-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide



Following the procedure in Step C of Example 60, 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-3-methyl-1*H*-imidazol-3-ium triflate (630 g, 1.0 mmol) was reacted with 1*H*-pyrazole-3-carbaldehyde (288 mg, 3.0 mmol), after being purified by silica gel chromatography, to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-3-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide (320 mg, 70 %). MS (ESI) $(M+H)^+$ 460.0.

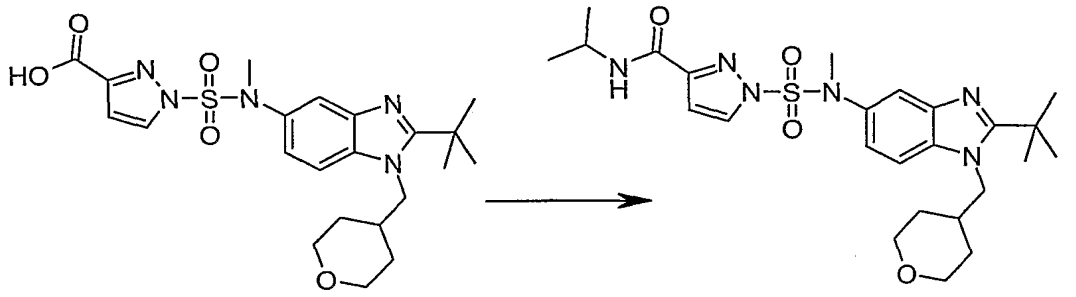
Step C. 1-[[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-3-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide (320 mg, 0.7 mmol) and ozone (615 mg, 1.0 mmol) was heated in DMF (6 mL) at 50^{0}C for 4 hr. The resulting 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid solution in DMF was used directly in Step A. MS (ESI) $(M+H)^+$ 476.0.

Example 115

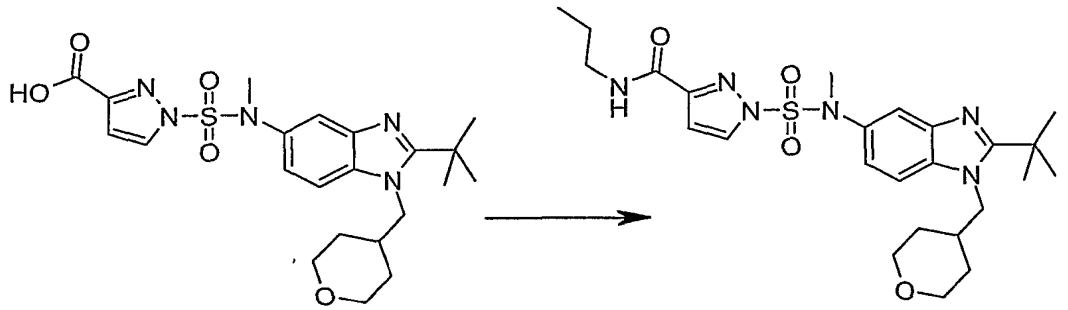
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropyl-1*H*-pyrazole-3-carboxamide



Following the procedure in Step A of Example 114, 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid (65 mg, 0.14 mmol) was reacted with isopropylamine (59 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropyl-1*H*-pyrazole-3-carboxamide (TFA salt, 31 mg, 36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 6.6 Hz, 6H), 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 3.33 (m, 2H), 3.56 (s, 3H), 3.91 (m, 2H), 4.20 (m, 1H), 4.51 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 2.8 Hz, 1H), 7.40 (dd, J = 9.0, 2.0 Hz, 1H), 7.53 (s, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$516.8.

Example 116

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-3-carboxamide

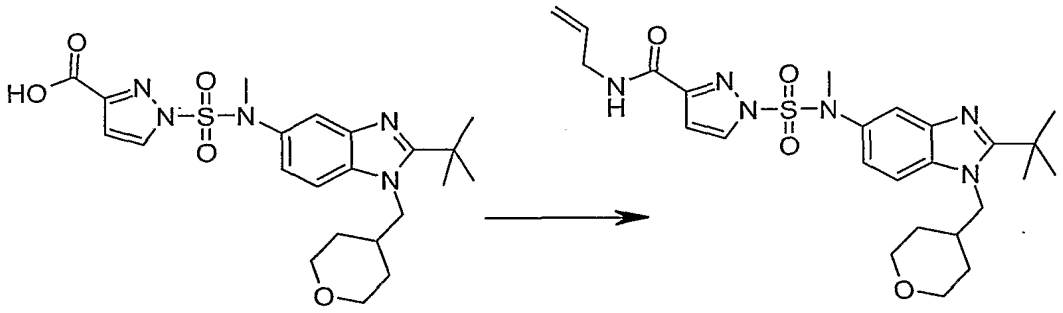


Following the procedure in Step A of Example 114, 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid (65 mg, 0.14 mmol) was reacted with propylamine (59 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-3-carboxamide (TFA salt, 26 mg,

30 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H), 1.52 (m, 4H), 1.62 (m, 2H), 1.65 (s, 9H), 2.33 (m, 1H), 3.28 (m, 2H), 3.33 (m, 2H), 3.58 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 2.8 Hz, 1H), 7.39 (dd, J = 9.0, 2.0 Hz, 1H), 7.53 (s, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$516.8.

Example 117

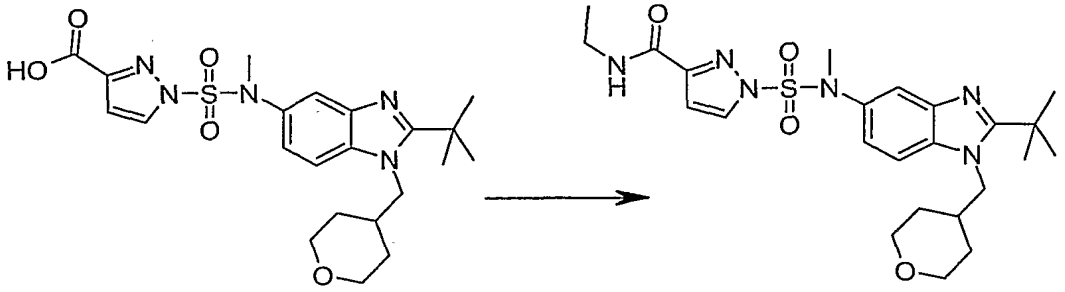
_N_-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-3-carboxamide



Following the procedure in Step A of Example 114, 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid (65 mg, 0.14 mmol) was reacted with allylamine (57 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide *N*-allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-3-carboxamide (TFA salt, 18 mg, 21 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.62 (m, 2H), 1.64 (s, 9H), 2.32 (m, 1H), 3.31 (m, 2H), 3.57 (s, 3H), 3.91 (m, 2H), 3.97 (d, J=5.3 Hz, 2H), (m, 1H), 4.49 (d, J = 7.6 Hz, 2H), 5.11 (m, 1H), 5.21 (m, 1H), 5,88 (m, 1H), 6.80 (d, J = 2.8 Hz, 1H), 7.39 (dd, J = 9.0, 2.0 Hz, 1H), 7.52 (s, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$514.8.

Example 118

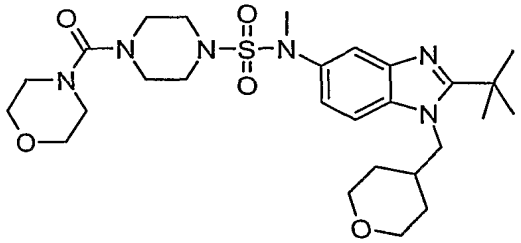
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-3-carboxamide



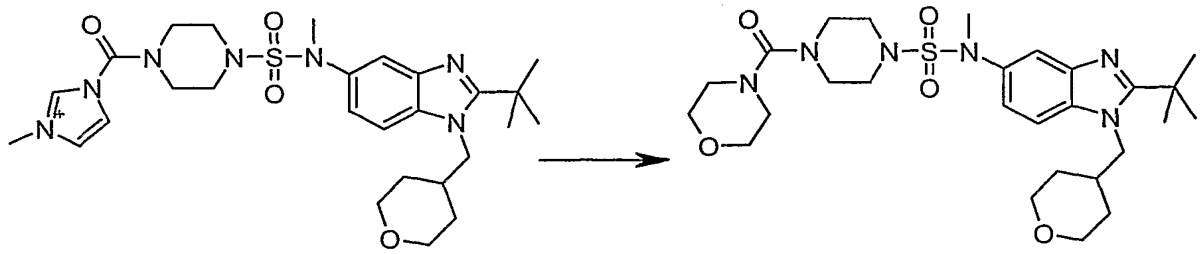
Following the procedure in Step A of Example 114, 1-[[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino](methylene)oxido-λ^4-sulfanyl]-1*H*-pyrazole-3-carboxylic acid (65 mg, 0.14 mmol) was reacted with ethylamine (45 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-3-carboxamide (TFA salt, 30 mg, 36 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 7.4 Hz, 3H), 1.52 (m, 4H), 1.65 (s, 9H), 2.33 (m, 1H), 3.32 (m, 2H), 3.40 (q, J =7.4 Hz, 2H), 3.58 (s, 3H), 3.91 (m, 2H), 4.51 (d, J = 7.6 Hz, 2H), 6.80 (d, J = 2.8 Hz, 1H), 7.40 (dd, J = 9.0, 2.0 Hz, 1H), 7.53 (s, 1H), 7.88 (d, J = 2.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H); MS (ESI) $(M+H)^+$502.8.

Example 119

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)piperazine-1-sulfonamide**

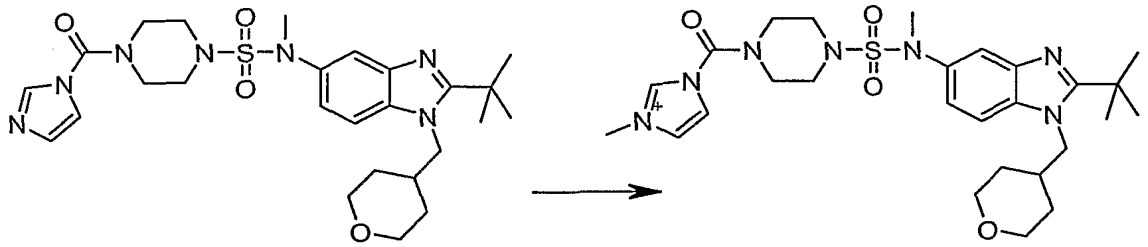


Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)piperazine-1-sulfonamide



A solution of 1-[(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate (20 mg, 0.03 mmol), morpholine (87 mg, 1 mmol), and Hunig's base (0.2 mL) in MeCN (2 mL) was stirred overnight at r.t. The reaction mixture was then condensed to give a residue, which was purified by reverse phase HPLC to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)piperazine-1-sulfonamide (TFA salt, 5 mg, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 4H), 1.68 (s, 9H), 1.83 (m, 4H), 2.37 (m, 1H), 3.25 (m, 8H), 3.29 (m, 6H), 3.33 (s, 3H), 3.62 (m, 4H), 3.93 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 7.69 (d, J=9.2 Hz, 1H), 7.81 (s, 1H), 7.97 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$562.8.

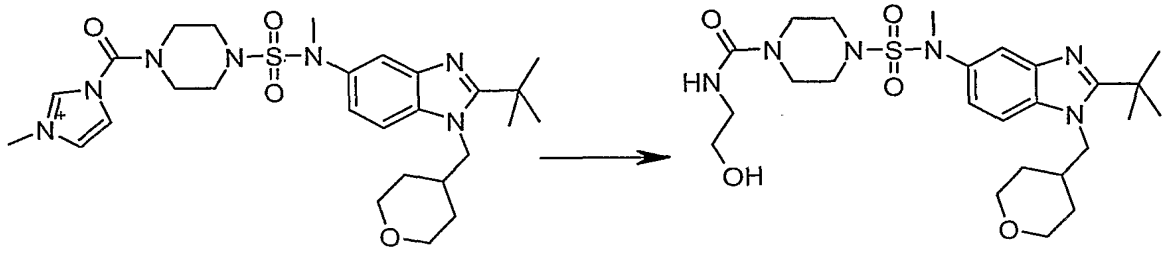
Step B. 1-[(4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(1*H*-imidazol-1-ylcarbonyl)-*N*-methylpiperazine-1-sulfonamide (1.09 g, 2.0 mmol) in acetonitrile (20 mL) was treated with methyl trifluoromethanesulfonate (1.0 g, 6.0 mmol) at r.t for 0.5 hr. The resulting 1-[(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate solution in MeCN was used in the step A directly.

Example 120

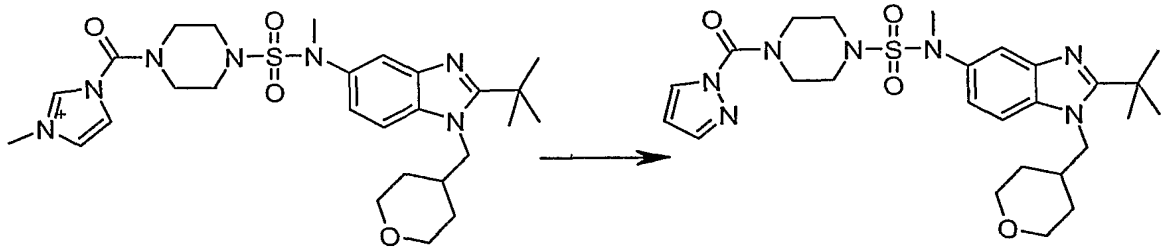
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperazine-1-carboxamide



Following the procedure in Step A of Example 119, 1-[(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate (40 mg, 0.06 mmol) was reacted with 2-aminoethanol (61 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperazine-1-carboxamide (TFA salt, 19 mg, 52 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 4H), 1.68 (s, 9H), 2.37 (m, 1H), 3.24 (m, 8H), 3.33 (s, 3H), 3.40 (m, 4H), 3.55 (m, 2H), 3.93 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 7.69 (d, J=9.2 Hz, 1H), 7.82 (s, 1H), 7.97 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$536.8.

Example 121

***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-pyrazol-1-ylcarbonyl)piperazine-1-sulfonamide**

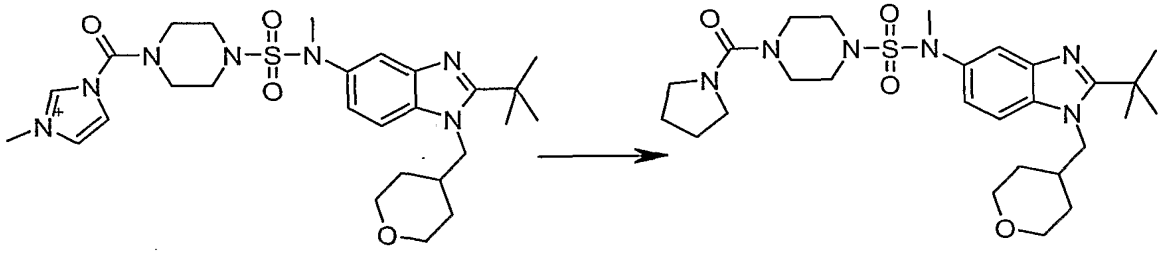


Following the procedure in Step A of Example 119, 1-[(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate (40 mg, 0.06 mmol) was reacted with 1*H*-pyrazole (68 mg, 1.0 mmol), after

being purified by reverse phase HPLC to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-pyrazol-1-ylcarbonyl)piperazine-1-sulfonamide (TFA salt, 29 mg, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (m, 4H), 1.68 (s, 9H), 2.37 (m, 1H), 3.35 (m, 9H), 3.81 (m, 4H), 3.93 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 6.44 (m, 1H), 7.68 (s, 1H), 7.69 (d, J=9.2 Hz, 1H), 7.84 (s, 1H), 7.97 (d, J=9.2 Hz, 1H), 8.11 (s, 1H); MS (ESI) $(M+H)^+$543.8.

Example 122

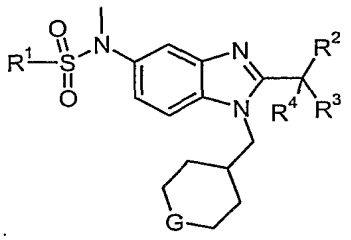
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylcarbonyl)piperazine-1-sulfonamide**



Following the procedure in Step A of Example 119, 1-[(4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazin-1-yl)carbonyl]-3-methyl-1*H*-imidazol-3-ium triflate (40 mg, 0.06 mmol) was reacted with pyrrolidine (71 mg, 1.0 mmol), after being purified by reverse phase HPLC to provide *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylcarbonyl)piperazine-1-sulfonamide (TFA salt, 26 mg, 70 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (m, 4H), 1.68 (s, 9H), 1.83 (m, 4H), 2.37 (m, 1H), 3.25 (m, 8H), 3.34 (m, 9H), 3.93 (m, 2H), 4.54 (d, J = 7.6 Hz, 2H), 7.69 (d, J=9.2 Hz, 1H), 7.82 (s, 1H), 7.97 (d, J=9.2 Hz, 1H); MS (ESI) $(M+H)^+$547.0.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O-, -CHF-, and –CF_2-;

R^1 is a C_{2-6}heterocyclyl, wherein said C_{2-6}heterocyclyl includes at least one nitrogen on said C_{2-6}heterocyclyl ring, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{2-6}heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxy, R^5-C(=O)-, R^5-C(=O)-NH-, R^5R^6-NH-C(=O)-, R^5R^6-NH-C(=O)-NH-, R^5-O-C(=O)-, R^5-O-C(=O)-NH-, C_{1-6}alkoxy, and C_{1-6}alkylamino, wherein said R^5, R^6 are independently selected from –H, C_{1-6}alkyl, C_{6-10}aryl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, C_{2-6}heterocyclyl, halogenated C_{1-6}alkyl, and hydroxy-C_{1-6}alkyl; and

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

2. A compound as claimed in claim 1, wherein

G is selected from –O- and –CF_2-;

R^1 is a C_{2-6}heterocycloalkyl, wherein said C_{2-6}heterocycloalkyl includes at least one nitrogen on said C_{2-6}heterocycloalkyl ring, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{2-6}heterocycloalkyl is optionally substituted with one or more groups selected from halogen, hydroxy, R^5-C(=O)-, R^5-C(=O)-NH-, R^5R^6-NH-C(=O)-, R^5R^6-NH-C(=O)-NH-, R^5-O-C(=O)-, R^5-O-C(=O)-NH-, C_{1-6}alkoxy, and C_{1-6}alkylamino, wherein said R^5, R^6 are independently selected from –H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, C_{2-5}heterocycloalkyl, halogenated C_{1-6}alkyl, and hydroxy-C_{1-6}alkyl; and

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

3. A compound as claimed in claim 1, wherein

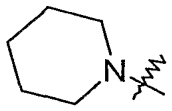
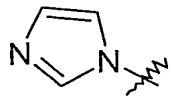
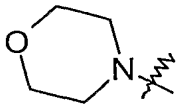
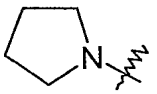
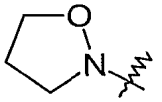
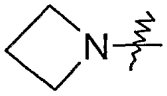
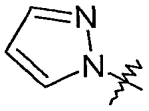
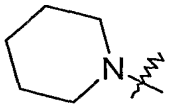
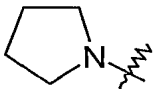
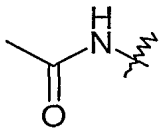
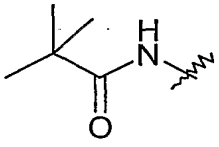
G is selected from –O- and –CF_2-;

R^1 is selected from piperidinyl, imidazolyl, pyrrolyl, pyrazolyl, morpholinyl, pyrrolidinyl, azetidinyl, and isoxazolidinyl, wherein said piperidinyl, imidazolyl, pyrrolyl, pyrazolyl, morpholinyl, pyrrolidinyl, azetidinyl, and isoxazolidinylare optionally substituted with one or more groups selected from fluoro and C_{2-5}acylamino;

R^2, R^3 and R^4 are selected from fluoro and methyl with a proviso that R^2, R^3 and R^4 are the same.

4. A compound as claimed in claim 1, wherein

G is selected from –O- and –CF_2-;

R^1 is selected from  ,  ,  ,  ,  ,  and  ; wherein said  and  are optionally substituted by one or more groups selected from fluoro,  and  ; and

R^2, R^3 and R^4 are selected from fluoro and methyl with a proviso that R^2, R^3 and R^4 are the same.

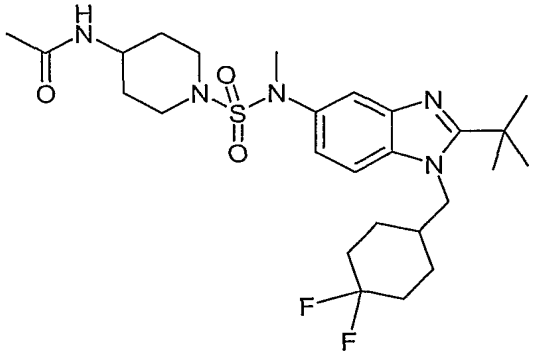
5. A compound as claimed in claim 1, wherein

G is selected from –O- and –CF_2-;

R^1 is selected from C_{3-5}heterocycloalkyl and C_{2-5}heteroaryl, wherein said C_{3-5}heterocycloalkyl or C_{2-5}heteroaryl includes at least one nitrogen on said C_{3-5}heterocycloalkyl or C_{2-5}heteroaryl rings, respectively, one of said at least one

nitrogen is directly linked to the sulfonyl group of formula I, and said C_{3-5}heterocycloalkyl and C_{2-5}heteroaryl are optionally substituted with one or more groups selected from halogen, C_{1-3}alkoxy, C_{1-3}alkylamino, and C_{2-5}acylamino; R^2, R^3 and R^4 are independently selected from fluoro and methyl.

6. A compound selected from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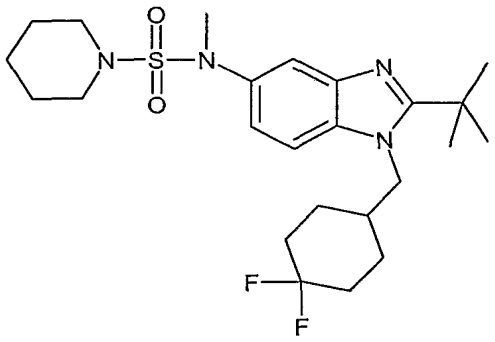
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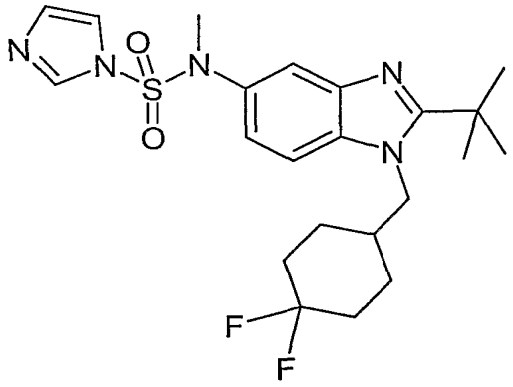
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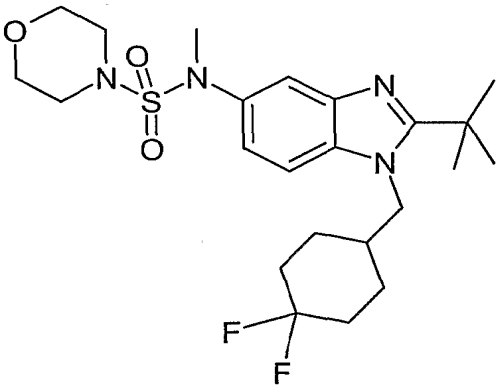
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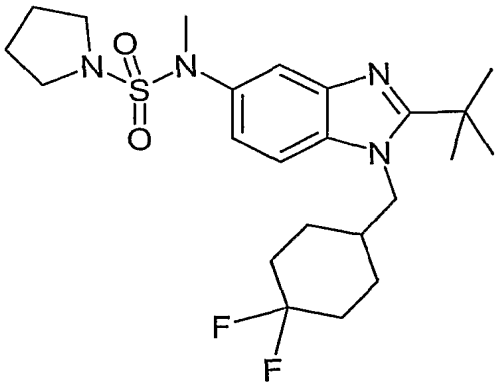
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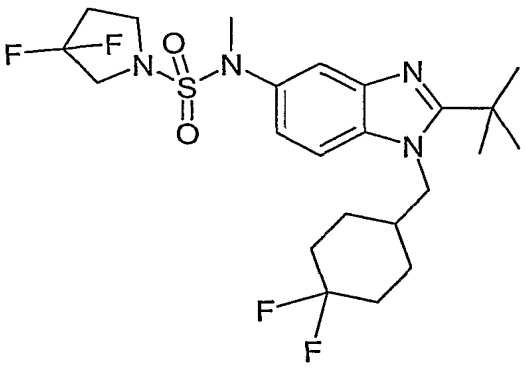
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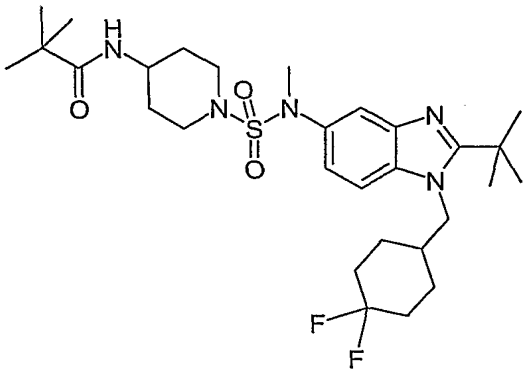
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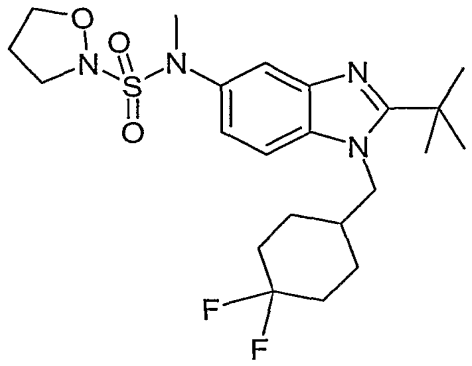
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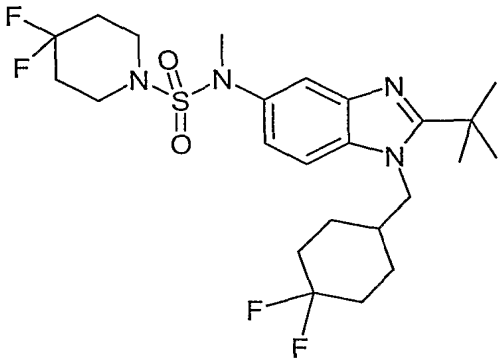
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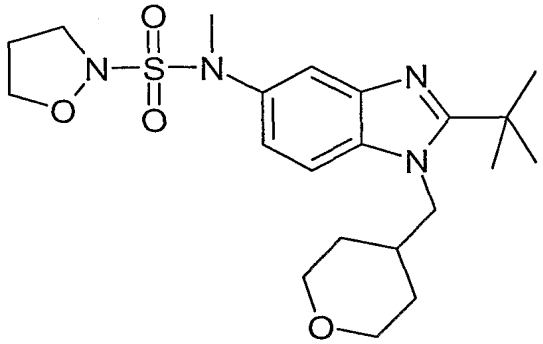
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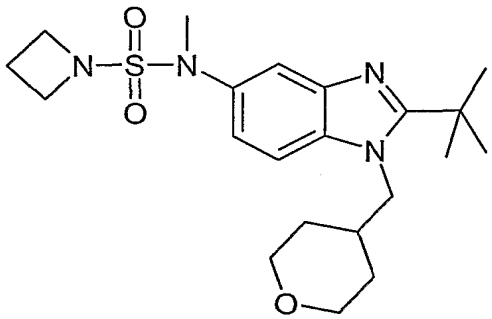
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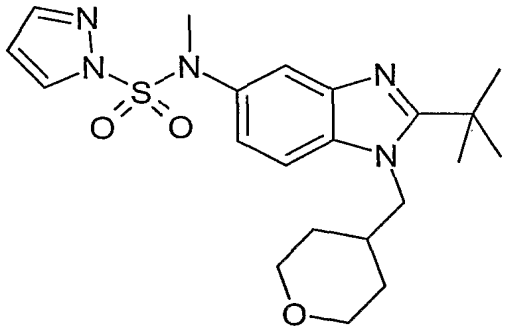
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and pharmaceutically acceptable salts thereof.

7. A compound selected from:

N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpyrrolidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylmorpholine-4-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperidine-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpiperidine-1-sulfonamide;

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylisoxazolidine-2-sulfonamide;

N-(1-{[[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-pyrrolidin-1-ylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-1*H*-pyrrol-1-ylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperidine-4-carboxamide;

N-(*tert*-butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-diethylpiperidine-4-carboxamide;

1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperidine-4-carboxamide;
N-butyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2,2,2-trifluoroethyl)piperidine-4-carboxamide;
N-allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isobutylpiperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxy-1-methylethyl)piperidine-4-carboxamide;
1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperidine-4-carboxamide;
Ethyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclopropanecarboxamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)-2-methylpropanamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)cyclobutanecarboxamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)butanamide;
N-(1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)propanamide;
Methyl 1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidine-3-carboxylate;
N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]hexahydro-*N*-methyl-1*H*-azepine-1-sulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-*N*,4-dimethyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-(hydroxymethyl)-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-hydroxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-4-methoxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-(1,1-dimethylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-benzimidazol-5-yl]-3-hydroxy-*N*-methyl-1-piperidinesulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylazetidine-1-sulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4,4-difluoro-N-methylpiperidine-1-sulfonamide;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-3,3-difluoro-N-methylpyrrolidine-1-sulfonamide;

Methyl 1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidine-4-carboxylate;

N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

(4R)-N-[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-4-hydroxy-N,4-dimethylisoxazolidine-2-sulfonamide;

N-(1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)acetamide;

N-(1-{[[2-tert-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl](methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide;

tert-Butyl [1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]carbamate

tert-Butyl 4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxylate;

4-{[(Cyclopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide;

N-cyclopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide;
4-{[(isopropylamino)carbonyl]amino}-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperidine-1-sulfonamide;
N-isopropyl-4-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperazine-1-carboxamide;
N-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]acetamide;
2,2-Dimethyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide;
2-Methyl-*N*-[1-({methyl[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]amino}sulfonyl)piperidin-4-yl]propanamide;
4-Acetyl-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide;
4-(2,2-Dimethylpropanoyl)-*N*-methyl-*N*-[1-(tetrahydro-2*H*-pyran-4-ylmethyl)-2-(trifluoromethyl)-1*H*-benzimidazol-5-yl]piperazine-1-sulfonamide;
N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)acetamide;
N-(1-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperidin-4-yl)-2,2-dimethylpropanamide;
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylmorpholine-4-sulfonamide;
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylpyrrolidine-1-sulfonamide;
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-3,3-difluoro-*N*-methylpyrrolidine-1-sulfonamide;
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylisoxazolidine-2-sulfonamide;
N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4,4-difluoro-*N*-methylpiperidine-1-sulfonamide;
tert-Butyl 4-{[{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}piperazine-1-carboxylate;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide;

4-{[{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}(methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-4-{[(methylamino)carbonyl]amino}piperidine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]-N-methylisoxazolidine-2-sulfonamide;

4-Acetyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(2,2-dimethylpropanoyl)-*N*-methylpiperazine-1-sulfonamide;

4-Benzoyl-*N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(3-methylbutanoyl)piperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclopropylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-propionylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-isobutyryl-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(cyclobutylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-butyryl-*N*-methylpiperazine-1-sulfonamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopentylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclobutylpiperazine-1-carboxamide;

N-(*tert*-Butyl)-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

N-butyl-4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

N-Allyl-4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propylpiperazine-1-carboxamide;

4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(cyclopropylmethyl)piperazine-1-carboxamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(1*H*-imidazol-1-ylcarbonyl)-*N*-methylpiperazine-1-sulfonamide;

Isopropyl 4-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}piperazine-1-carboxylate;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)acetamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}pyrrolidin-3-yl)-2,2-dimethylpropanamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}azetidin-3-yl)acetamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-imidazole-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,4-triazole-1-sulfonamide;

N-{2-*tert*-Butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methyl-1*H*-1,2,3-triazole-1-sulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-pyrazole-1-sulfonamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-4-carboxamide;

N-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*,*N*-dimethyl-1*H*-pyrazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-methyl-1*H*-pyrazole-4-carboxamide;

N-(*tert*-Butyl)-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-4-carboxamide;

N-(1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazol-3-yl)acetamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methyl-1*H*-imidazole-1-sulfonamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-imidazole-4-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-cyclopropyl-1*H*-pyrazole-3-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-isopropyl-1*H*-pyrazole-3-carboxamide;

1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-propyl-1*H*-pyrazole-3-carboxamide;
N-Allyl-1-{[[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-1*H*-pyrazole-3-carboxamide;
1-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-ethyl-1*H*-pyrazole-3-carboxamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylcarbonyl)piperazine-1-sulfonamide;
4-{[[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl](methyl)amino]sulfonyl}-*N*-(2-hydroxyethyl)piperazine-1-carboxamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-pyrazol-1-ylcarbonyl)piperazine-1-sulfonamide;
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylcarbonyl)piperazine-1-sulfonamide;
and pharmaceutically acceptable salts thereof.

8. A compound according to any one of claims 1-7 for use as a medicament.

9. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the therapy of pain.

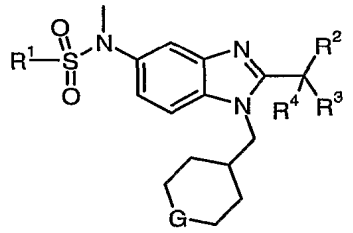
10. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the treatment of anxiety disorders.

11. The use of a compound according to any one of claims 1-7 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

12. A pharmaceutical composition comprising a compound according to any one of claims 1-7 and a pharmaceutically acceptable carrier.

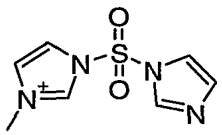
13. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-7.

14. A method for preparing a compound of Formula I, comprising the steps of:

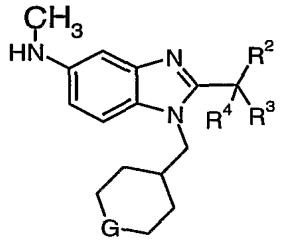


I

a) reacting a compound of Formula II with a compound of formula III,



II



III

b) treating reaction product of step a) with MeOTf;

c) reacting reaction product of step b) with R^1H,

wherein

G is selected from –O-, -CHF-, and $–CF_2$-;

R^1 is a C_{2-6}heterocyclyl, wherein said C_{2-6}heterocyclyl includes at least one nitrogen on said C_{2-6}heterocyclyl ring, one of said at least one nitrogen is directly linked to the sulfonyl group of formula I, and said C_{2-6}heterocyclyl is optionally substituted with one or more groups selected from halogen, hydroxy, R^5-C(=O)-, R^5-C(=O)-NH-, R^5R^6-NH-C(=O)-, R^5R^6-NH-C(=O)-NH-, R^5-O-C(=O)-, R^5-O-C(=O)-NH-, C_{1-6}alkoxy, and C_{1-6}alkylamino, wherein said R^5, R^6 are independently selected from –H, C_{1-6}alkyl, C_{6-10}aryl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, C_{2-6}heterocyclyl, halogenated C_{1-6}alkyl, and hydroxy-C_{1-6}alkyl; and

R^2, R^3 and R^4 are independently selected from fluoro and methyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001405

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005030761 A1 (ASTRAZENECA UK LIMITED), 7 April 2005 (07.04.2005), abstract, pages 142-145	1
P,A	--	2-14
P,X	WO 2005030733 A1 (ASTRAZENECA UK LIMITED), 7 April 2005 (07.04.2005), abstract, pages 62-65	1
P,A	--	2-14
A	US 20040116465 A1 (CHENG ET AL), 17 June 2004 (17.06.2004), paragraph [0001]-[0003], examples 95-96	1-14
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2005	30-11-2005
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001405

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 20020006948 A1 (HALFBRODT ET AL), 17 January 2002 (17.01.2002), paragraph [0383], example 143,160,244 --	1-14
P,A	WO 2005021547 A2 (PHARMAXIS PTY LTD.), 10 March 2005 (10.03.2005) --	1-14
A	HOLENZ JÖRG ET AL, "Medicinal Chemistry Driven Approaches Toward Novel and Selective Serotonin 5-HT6 Receptor Ligands", J.Med.Chem. 2005, Vol. 48, p. 1781-1795, table1, compound 16, abstract -- --------	1-14

Continuation of cover sheet

C07D 401/12 (2006.01)
A61K 31/4184 (2006.01)
A61P 25/22 (2006.01)
A61P 29/02 (2006.01)
C07D 413/12 (2006.01)
C07D 413/14 (2006.01).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001405

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 13 relate to a method of treatment of the human body by therapy /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

29/10/2005

International application No.
PCT/SE 2005/001405

WO	2005030761	A1	07/04/2005	SE	0302570	D	00/00/0000
WO	2005030733	A1	07/04/2005	SE	0302571	D	00/00/0000
US	20040116465	A1	17/06/2004	AU	7477201	A	14/01/2002
				BG	108271	A	30/12/2004
				CA	2414995	A	10/01/2002
				CA	2444381	A	31/10/2002
				CN	1503787	A	09/06/2004
				CZ	20032833	A	12/05/2004
				EE	200300524	A	16/02/2004
				EP	1307481	A	07/05/2003
				EP	1390350	A	25/02/2004
				HU	0303825	A	01/03/2004
				IL	158142	D	00/00/0000
				JP	2004502416	T	29/01/2004
				JP	2004528334	T	16/09/2004
				MX	PA03009558	A	12/02/2004
				NO	20034665	A	10/12/2003
				NZ	528403	A	27/05/2005
				PL	366517	A	07/02/2005
				SE	0101387	D	00/00/0000
				SK	13032003	A	03/01/2005
				WO	02085866	A	31/10/2002
				ZA	200307752	A	03/01/2005
				SE	524944	C	26/10/2004
				SE	0200769	A	15/09/2003
US	20020006948	A1	17/01/2002	AU	782993	B	15/09/2005
				AU	4233201	A	24/07/2001
				BG	106821	A	31/01/2003
				BR	0107628	A	08/10/2002
				CA	2396227	A	19/07/2001
				CN	1395568	A,T	05/02/2003
				CZ	20022420	A	16/10/2002
				EE	200200390	A	15/10/2003
				EP	1246808	A	09/10/2002
				HR	20020664	A	30/04/2005
				HU	0204011	A	28/05/2003
				IL	150150	D	00/00/0000
				JP	2003523961	T	12/08/2003
				MX	PA02005742	A	18/09/2002
				NO	20023362	A	13/09/2002
				NZ	519326	A	25/02/2005
				PL	356091	A	14/06/2004
				SK	10002002	A	04/02/2003
				WO	0151473	A	19/07/2001
				ZA	200206470	A	19/02/2004
WO	2005021547	A2	10/03/2005	NONE			